FALL 2018

biosupply trends
QUARTERLY

SPECIAL FOCUS:
INNOVATION

Artificial Intelligence

ENHANCING DIAGNOSTICS AND TREATMENT

CHANGING LIVES WITH
Cord Blood Transplants

UNDERSTANDING
Migraines

TREATING CHRONIC PAIN WITH
Medical Marijuana

The Growth of Biosimilars:
NEW THERAPEUTIC OPTIONS

SCIG for CIDP Maintenance Therapy p.46

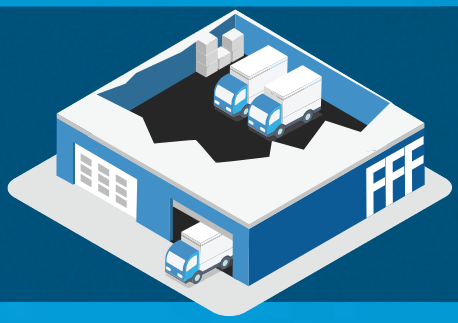
8 Critical Steps

Purchasing

At FFF, we only purchase products from the manufacturer–never from another distributor or source. This means the integrity of our products is never in question from tampering or mishandling.

Storage

We store and transport viable protein compounds that are sensitive to temperature variations. Temperature controlled, monitored 24/7, and supported with backup generators in the event of power loss.

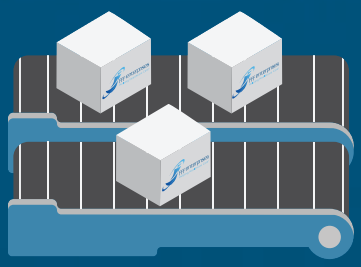


Specialty Packaging

We use only certified, qualified, environmentally-friendly packaging, taking extra precautions for frozen and refrigerated products.

Interactive Allocation

Assures responsible, demand-based distribution of critical-care products in challenging market conditions. Reduces potential for gray-market purchasing to accommodate critical demand issues.



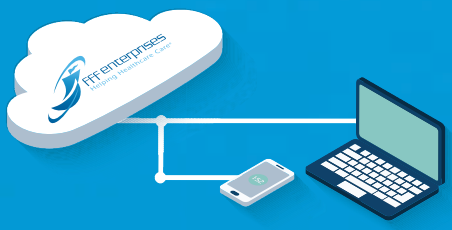
To Guaranteed Channel Integrity™

Delivery

We deliver only to facilities with a state-issued license, and only to the address on the license. We make no exceptions. It is our commitment to do everything in our power to prevent products from entering a secondary distribution channel.

Methods of Delivery

Monitoring and adjusting for extreme weather conditions allows time-sensitive delivery to ensure product integrity.



Verification

In compliance with DSCSA requirements, every product shipped from FFF is accompanied by a packing slip that includes information regarding the manufacturer and presentation, as well as the three T's: Transaction Information, Transaction History and Transaction Statement.

Tracking

To meet DSCSA requirements, FFF provides product traceability information on all packing slips. In addition, Lot-Track® electronically captures and permanently stores each product lot number, matched to customer information, for every vial of drug we supply.

Our commitment to a secure pharmaceutical supply chain is demonstrated by our flawless safety record.

FFF enterprises
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Since 1988

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About BioSupply Trends Quarterly

BioSupply Trends Quarterly is the definitive source for industry trends, news and information for healthcare professionals in the biopharmaceuticals marketplace.

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Exciting Advancements in Disease Diagnosis and Treatment

LOOKING BACK AT the history of medicine underscores just how far we have come — from making diagnoses "based on what ancient physicians could observe with their eyes and ears," to the development of the microscope that "revealed not only the cellular structure of human tissues, but also the organisms that cause disease," to the establishment of the clinical laboratory and the development of new biological treatments in the 20th century.[1] Today, modern methods of diagnosing and treating diseases continue to make exciting advances, several of which we highlight in this issue.

Some tout artificial intelligence (AI) as the future of medicine. As we explore in our article "Artificial Intelligence and Big Data — A Crossroads of Interoperability and Capability," there are different forefronts of AI. One, known as "deep learning," provides the potential for machines to learn via repetition to detect diseases far more accurately and faster than could ever be possible by humans. Another, known as the "deep patient," allows machines to sift through vast amounts of data and link comparative trends to help humans make decisions that will develop better roadmaps to care. But AI also comes with many unknowns — especially when looking at its capabilities for altering genes. Clearly, as AI moves forward, it will be necessary to scrutinize its ethical and legal ramifications.

Another area of treatment predicted to radically transform medical strategies over the next few decades is the use of cord blood in transplants. While cord blood was once considered a useless byproduct, it is now known to contain stem cells that can be harvested, stored and used to save the lives of people with more than 80 different diseases. In our article "The Future of Cord Blood," we explain the importance of cord blood for hematopoietic stem cell transplants. We also delve into cord blood's advantages and limitations, because while there is no denying it is lifesaving, especially for those with blood and immune system disorders and for ethnic minorities who are limited in locating potential bone marrow donors, its benefit in transplants for adults is hampered due to the small volume of stem cells collected in one cord blood unit. As such, considerable research is being conducted to expand the usefulness of cord blood transplants, as well as to assess its ability to treat a host of other diseases.

On another front, while not as favorable as generics in reducing the cost of drugs, biosimilars will undoubtedly have an impact, with many predicting a reduction in price by about one-third or more. Biosimilars have been widely available in Europe for more than a decade, and finally, the number of approvals in the U.S. is starting to make headway. Even so, manufacturers of biosimilars in the U.S. face many challenges, as we explain in our article "Biosimilars: From Concept to Reality." These include patient satisfaction and safety, demonstrating interchangeability and extrapolating indications. Nevertheless, biosimilars have support from payers and regulators, so it will be essential to create policy frameworks to ensure their continued approval.

As always, we hope you enjoy this issue of *BioSupply Trends Quarterly*, and find it both relevant and helpful to your practice.

Helping Healthcare Care,

Patrick M. Schmidt
Publisher

1. Berger D. A Brief History of Medical Diagnosis and the Birth of the Clinical Laboratory. MLO, July 1999. Accessed at www.academia.dk/Blog/wp-content/uploads/KlinLab-Hist/LabHistory1.pdf.

biosupply trends QUARTERLY

Our mission is to serve as the industry's leading resource for timely, newsworthy and critical information impacting the biopharmaceuticals marketplace, while providing readers with useful tips, trends, perspectives and leading indicators on the topics pertinent to their business.

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CMS Launches New Voluntary Bundled Payment Model

In a continued move toward value-based care that shifts to information technologies that better manage care, risk and cost, the Centers for Medicare and Medicaid Services (CMS) has launched a new voluntary bundled payment model that qualifies as an advanced alternative payment model (APM) under its quality payment program (QPP). The new model, called Bundled Payments for Care Improvement (BPCI) Advanced, is part of the BPCI initiative developed by the Centers for Medicare and Medicaid Innovation to test innovative payment and service delivery models that could reduce Medicare, Medicaid and Children's Health Insurance Program expenses while preserving or enhancing the quality of care for beneficiaries. Participants will receive payments for performance on 32 different clinical episodes such as major joint replacement of the lower extremity (inpatient) and percutaneous coronary intervention (inpatient or outpatient).

"BPCI Advanced builds on the earlier success of bundled payment models and is an important step in the move away from fee-for-service and toward paying for value," said CMS Administrator Seema Verma. "In BPCI Advanced, participants will be expected to redesign care delivery to keep Medicare expenditures within a defined budget while maintaining or improving performance on specialty quality measures. Participants bear financial risk, have payments under the model tied to quality performance and are required to use Certified Electronic Health Record Technology." ❖

Slabodkin G. CMS Launches New Voluntary Bundled Payment Model. Health Data Management, Jan. 10, 2018. Accessed at www.healthdatamanagement.com/news/cms-launches-new-voluntary-bundled-payment-model.

HHS Loosens Restrictions on Short-Term Health Plans

A final rule issued by the U.S. Department of Health and Human Services (HHS) allows insurers to once again sell short-term health insurance for up to 12 months, as well as makes the plans renewable for up to three years. The rule overturns an Obama administration directive that limited these plans to 90 days. Short-term plans differ from other Affordable Care Act (ACA) plans because they can bar people with preexisting health conditions, limit coverage, set annual and lifetime caps on benefits, and cover fewer prescription drugs. Most exclude benefits for maternity care, preventive care, mental health services or substance abuse treatment.

Administration officials estimate short-term plan premiums could be half the cost of the more comprehensive ACA plans, and predict approximately 600,000 people will enroll in the plans in 2019, with 100,000 to 200,000 of those dropping ACA coverage to do so. Just over 14 million people are enrolled in ACA plans this year. According to a recent Congressional Budget Office (CBO) report, premiums for the average benchmark ACA plan rose by 34 percent in 2018. Factors driving the increase include medical inflation, but CBO also cited the administration's decision last fall to drop payments to insurers for lowering deductibles for certain low-income policyholders. The same report expects premiums for ACA plans to increase 15 percent in 2019, partly due to consumers being less likely to purchase coverage without the threat of a tax penalty. ❖

Appleby J. Trump Administration Loosens Restrictions on Short-Term Health Plans. *Kaiser Health News,* Aug. 1, 2018. Accessed at khn.org/news/trump-administration-loosens-restrictions-on-short-term-health-plans/?utm_campaign=KHN%3A%20Daily%20Health%20Policy%20Report&utm_source=hs_email&utm_medium=email&utm_content=64888976&_hsenc=p2ANqtz--5OhM5pXfdCB2BV-jYegaOtWozm4M6Quvtf9Sb6_rHveBb3vzZsSWdswS9QrDs326c6Dyk9Rxy3m1ggLf-HlnVUNQxZQ&_hsmi=64888976.

CMS Restores Risk Adjustment Program

After a brief suspension of the Centers for Medicare and Medicaid Service's (CMS) risk-adjustment program, the agency adopted an interim final rule to restore $10.4 billion in funding to insurers to help them provide coverage to sick and costly enrollees. The final rule makes no changes to the program other than restoring it. CMS cited its reason for stopping payments was a court ruling from a federal judge in New Mexico who found the administration had not fully justified its formula for dispensing the funds. "This rule will restore operation of the risk-adjustment program and mitigate some of the uncertainty caused by the New Mexico litigation," said CMS Administrator Seema Verma.

The risk-adjustment program is not funded by taxpayer dollars; rather, it is collected from insurers that have healthier enrollees overall and then given to insurers with sicker, more expensive enrollees to help cover their costs. ❖

Weixel N. Trump Admin Restarts Key ObamaCare Payments. *MSN News,* July 25, 2018. Accessed at www.msn.com/en-us/news/politics/trump-admin-restarts-key-obamacare-payments/ar-AAAnnCw.

FDA Introduces Biosimilar Action Plan

On July 18, the U.S. Food and Drug Administration (FDA) introduced its Biosimilar Action Plan (BAP) to help speed up approvals to enhance access to lower-cost biologics. With biologics representing 40 percent of all prescription drug spending, FDA says it is trying to better manage review and licensure pathways to facilitate competition and modernize policies to make review more efficient. According to Scott Gottlieb, FDA's commissioner, the BAP seeks to preserve the "balance between innovation and competition [through] efficient, predictable and science-based pathways for drug review."

Specifically, the BAP focuses on four areas: efficiency of development and approval; scientific and regulatory clarity; effective communication; and reducing gaming of FDA requirements or other delays in competition. As part of the BAP, FDA is:

- Developing and implementing new FDA review tools such as standardized review templates for biosimilar and interchangeable products;
- Creating information resources and development tools for biosimilar sponsors;
- Enhancing the *Purple Book* to make it more useful;
- Exploring data-sharing agreements with foreign regulatory authorities to facilitate increased use of non-U.S.-licensed comparator products;
- Establishing an Office of Therapeutic Biologics and Biosimilars;
- Continuing to provide education to healthcare professionals about biosimilar and interchangeable products;
- Publishing guidance on biosimilar product labeling;
- Providing additional clarity on demonstrating interchangeability;
- Providing additional support to product developers regarding product quality and manufacturing processes; and
- Engaging in public dialogue about the biosimilar program.

Additionally, FDA has committed to holding public meetings and hearings, as well as prioritizing the development of guidance on various aspects of the Biologics Price Competition and Innovation Act. ❖

Koblitz SW. Biosimilar Action Plan Introduced to Kick-Start the Biosimilar Market. U.S. Food and Drug Administration Law Blog, July 20, 2018. Accessed at www.fdalawblog.net/2018/07/biosimilar-action-plan-introduced-to-kick-starting-the-biosimilar-market.

CMS Proposes Paying for Telehealth and Overhauling Medicare Billing

The Centers for Medicare and Medicaid Services (CMS) is proposing a plan to pay doctors for virtual visits and overhaul Medicare billing standards put in place in the 1990s.

For telehealth, doctors would be paid for their time spent reaching out to beneficiaries via telephone or other telecommunications devices to decide whether an office visit or other service is needed, as well as when they review a video or image sent by a patient seeking care or diagnosis. "This is a big issue for [the] elderly and disabled population for which transportation can be a barrier to care," said CMS Administrator Seema Verma. "We're not intending to replace office visits, but rather to augment them and create new access points for patients."

With current Medicare billing standards, doctors bill Medicare for patient visits using a set of codes that distinguish level of complexity and site of care. Instead, CMS is proposing allowing practitioners to designate the level of a patient's care needs using their medical decisionmaking or time spent with the patient rather than applying the coding. In addition, CMS seeks to eliminate the requirement to justify the medical necessity of a home visit in lieu of an office visit, and is considering eliminating a policy that prevents payment for same-day visits with multiple practitioners in the same specialty within a group practice. "Today's proposals deliver on the pledge to put patients over paperwork by enabling doctors to spend more time with their patients," Verma said in a statement. "Physicians tell us they continue to struggle with excessive regulatory requirements and unnecessary paperwork that steal time from patient care. This administration has listened and is taking action." ❖

Dickson V. CMS Proposes to Overhaul Medicare Billing Standards, Pay for Telehealth. MTelehealth, July 12, 2018. Accessed at www.mtelehealth.com/cms-proposes-to-overhaul-medicare-billing-standards-pay-for-telehealth.

Proposed 2019 OPPS Rules

By Bonnie Kirschenbaum, MS, FASHP, FCSHP

THE LONG-AWAITED proposed 2019 Outpatient Prospective Payment System (OPPS) rules have been published in the *Federal Register* and will take effect on Jan. 1. As anticipated, the focus is on a patient-driven healthcare system with reimbursement across the episodic care journey rather than on single encounters in a healthcare facility. The proposed payment rule set has several prominent themes for the pharmacy sector: 1) simplify electronic health record requirements, reporting and regulations, 2) cut costs and save money and 3) address the opioid crisis.

Paying for Part B Drugs Under OPPS

Part B drugs are those used in an outpatient setting pursuant to a physician's order and are usually injectables. The Centers for Medicare and Medicaid Services (CMS) pays for Part B drugs in five different ways divided into two categories: 1) separately payable with line-item reimbursement and 2) not separately payable without line-item reimbursement (since they're paid as part of a bundle/package). Regardless of where the drug falls in these categories, it's essential to bill for each and every drug. CMS uses claims information to set rates in future years and makes them available to big data pools for analytic purposes. Any missing or erroneous data skews the accuracy of the pools and leads to faulty pathway development or decision-making.

In the first category (separately payable), these include:

1) New drugs not yet assigned a unique Healthcare Common Procedure Coding System code

2) New pass-through drugs, biologicals and radiopharmaceuticals (status indicator [SI] G)

3) Specified covered outpatient drugs (SI K)

In the second category (not separately payable) (SI N), these include:

4) Lower-cost packaged products costing (proposed) less than $125 per day (up from $120 in 2018)

5) Regardless of cost, products used in policy packaged services.

Payment for all packaged drugs, biologicals and radiopharmaceuticals is included in the services and procedures with which they are reported. These include:

- All diagnostic radiopharmaceuticals
- All contrast agents
- Anesthesia drugs
- Implantable biologicals that are surgically inserted or implanted into the body through a surgical incision or natural orifice
- Drugs, biologicals and radiopharmaceuticals that function as supplies when used in a diagnostic test or procedure
- Drugs and biologicals that function as supplies or implantable devices in a surgical procedure

Average sales price (ASP) for these drugs can vary from one quarter to another, and this year, CMS is proposing to change SIs to reflect a shift from SI K to SI N and back again as needed.

OPPS 2019 Proposed Payment

Transitional pass-through status: Non-pass-through separately payable drugs will continue to be paid for at ASP plus 6 percent (minus 2 percent sequestration). Some of these will expire in the quarter that is as close to three full years as possible after the products were first covered with pass-through payment status. The proposed rule lists 45 drugs with new/continuing pass-through status and 23 that lose pass-through payment status and move from SI G (pass-through) to SI K (separately payable) or SI N (items and services packaged into ambulatory payment classification [APC] rates). For 2019, new drugs and biologicals will be paid at wholesale acquisition cost (WAC) plus 3 percent (rather than WAC plus 6 percent) before ASP is available. If WAC is not available, CMS will continue to pay 95 percent of average wholesale price (AWP). Proposed provisions reducing transitional pass-through payments for policy-packaged drugs, biologicals and radiopharmaceuticals to offset costs packaged into APC groups is being developed for diagnostics and skin substitutes, and will be published by CMS as decisions are made.

Drugs and biologicals: The threshold for drugs and biologicals that are separately payable has increased to $125 per day based on ASP, an increase of $5 over this year. These will continue to be paid at ASP plus 6 percent (minus 2 percent sequestration) under the statutory default payment policy adopted in 2013. CMS will pay all non-pass-through separately payable therapeutic radiopharmaceuticals at ASP plus 6 percent (minus 2 percent sequestration) as well. However, radiopharmaceutical manufacturers are not required to submit ASP (although some manufacturers do voluntarily submit data, and CMS will use if for a patient-ready dose). If ASP data are not available, CMS will base payment on mean unit cost from its claims data.

To respond to these changes, pharmacy providers should ensure all drugs with SIs G, K and N are billed regardless of whether they are separately payable. The updated addendum B (a voluminous Excel spreadsheet that is updated quarterly throughout the year) will be published later this fall and will indicate the status indicators of Part B drugs and their

payment rates. One of the simplest ways to use it is to sort the SI column and look only at SI G, K and N drugs. In addition, pharmacy providers should prepare for changes in their list of waste billing drugs by determining which on the current list have moved from K to N status and will no longer be eligible for waste billing as of Jan. 1.

Payment rate changes for certain Medicare Part B drugs purchased by hospitals through 340B: Understanding what is proposed is essential before working on any statistics or predictions. First and foremost, this is not a Health Resources and Services Administration rule change, although many administrative changes to the 340B program are anticipated in the new year. These OPPS changes apply only to Medicare patients treated in an OPPS setting.

The proposed 2019 OPPS rules retain the 2018 rates that cut reimbursement for 340B facilities, as well as the modifier requirement that is the trigger to identify drugs with rate cuts. Products acquired under 340B and used in an outpatient setting for Medicare-eligible patients will continue to be paid at ASP minus 22.5 percent, WAC minus 22.5 percent or 69.46 percent of AWP, as applicable. Remember that OPPS reimburses in five different ways (pass-through before and after ASP is established, separately payable, and bundled or packaged either due to cost or statute). Only separately payable drugs (SI K) are affected; drugs on pass-through status (SI G) and vaccines continue to be excluded. Nonexcepted, off-campus hospital departments defined as outpatient facilities located away from the hospital's main facility paid under physician fee service (PFS) will also be subject to the reduction in 2019 and will be paid ASP minus 22.5 percent for drugs acquired through the 340B program. This is a change from this year when they were the exception to the payment cut rule. Also remember that CMS covers 80 percent of the payment with the remaining 20 percent the patient's responsibility, either out of pocket or through secondary insurance. When payment rates decrease, this positively affects patients by lowering their costs.

Biosimilar products in 2019: There are no proposed changes to the 2018 CMS revised payment policy for biosimilar products that established separate coding and a separate payment rate for each biosimilar product, even if they have the same biological reference product as another biosimilar product. All biosimilar biological products are eligible for pass-through status, not just the first biosimilar for a reference product. Biosimilar products purchased under 340B also are subject to the payment cuts.

"The proposed 2019 OPPS rules retain the 2018 rates that cut reimbursement for 340B facilities, as well as the modifier requirement that is the trigger to identify drugs with rate cuts."

Responding to the Opioid Crisis

In response to recommendations from the President's Commission on Combating Drug Addiction and the Opioid Crisis, the proposed rule set contains extensive discussions of practice changes that could be beneficial. For example, CMS is proposing to unpackage and pay separately for the cost of non-opioid pain management drugs that function as surgical supplies when they are furnished in the ambulatory surgery center setting in 2019. An equitable payment adjustment in the form of an add-on payment for APCs that use a non-opioid pain management drug, device or service is also being discussed, with Exparel as an example. In other rules, CMS is proposing getting rid of pain-management questions from Hospital Consumer Assessment of Healthcare Providers and Systems in response to the opioid epidemic.

Also of interest to pharmacies are the proposed site-neutral payments under which hospital clinic visits will be reimbursed at the same rate as physician offices and other ambulatory facilities. The PFS rule proposes telehealth/virtual care reimbursement that will offer many new opportunities. ❖

BONNIE KIRSCHENBAUM, MS, FASHP, FCSHP, is a freelance healthcare consultant with senior management experience in both the pharmaceutical industry and the pharmacy section of large corporate healthcare organizations and teaching hospitals. She has an interest in reimbursement issues and in using technology to solve them. Kirschenbaum is a recognized industry leader in forging effective alliances among hospitals, physicians, pharmaceutical companies and distributors and has written and spoken extensively in these areas.

Sources

1. CMS Proposes Medicare Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System Changes for 2019 (CMS-1695-P). Accessed at www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2018-Fact-sheets-items/2018-07-25.html.
2. Billing Code 4120-01-P. Accessed at s3.amazonaws.com/public-inspection.federalregister.gov/2018-15958.pdf.

Guidelines

Flu Vaccine Recommendations Updated by CDC and AAP

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices has updated its 2017-18 recommendations regarding the use of seasonal influenza (flu) vaccines and guidance for vaccine providers about the use of flu vaccines for the 2018-19 season. These include:

1) The vaccine virus composition for 2018-19 U.S. seasonal influenza vaccines;

2) A recommendation for the 2018-19 season that the live-attenuated influenza vaccine is an option for flu vaccination of persons for whom it is appropriate;

3) A recommendation that persons with a history of egg allergy may receive any licensed, recommended and age-appropriate influenza vaccine; and

4) Recent regulatory actions, including new vaccine licensures and labeling changes for previously licensed vaccines.

The complete set of recommendations can be viewed at www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_e.

In addition, the American Academy of Pediatrics (AAP) issued its annual flu recommendations that state all children ages 6 months and older should receive the influenza vaccine as soon as it becomes available. With 179 flu-related deaths in the 2017-18 season, AAP said the vaccine "significantly reduces a child's risk of severe influenza and death." "The flu virus is common and unpredictable," said Flor M. Munoz, MD, FAAB, member of the AAP Committee on Infectious Diseases. "Being immunized reduces the risk of a child being hospitalized due to flu." ❖

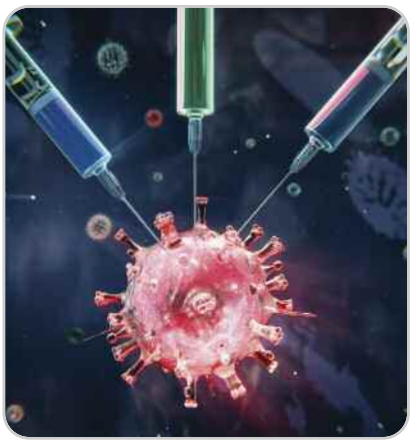
Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2018–19 Influenza Season. Centers for Disease Control and Prevention, Aug. 24, 2018 Accessed at www.cdc.gov/mmwr/volumes/67/rr/rr6703a1.htm?s_cid=rr6703a1_e.

AAP Issues Flu Vaccine Recommendations for 2018-2019. American Academy of Pediatrics press release, Sept. 3, 2018. Accessed at www.aap.org/en-us/about-the-aap/aap-press-room/Pages/AAP-Issues-Flu-Vaccine-Recommendations-for-2018-2019.aspx.

Influenza

FDA Chooses Influenza Vaccine Strains for the 2018-19 Season

In March, the U.S. Food and Drug Administration's (FDA) Vaccines and Related Biological Products Advisory Committee chose the Northern Hemisphere's 2018-19 influenza (flu) vaccine strains based on the World Health Organization's recommendations. For the trivalent vaccine, the committee voted unanimously to include an A/Michigan/45/2015 (H1N1) pdm09-like virus and an A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, the latter of which is a change from the 2017-18 vaccine. And, the committee voted 11-1 to include a B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage), which is also a change from the 2017-18 vaccine. The committee also voted unanimously to include a B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) as the second influenza B strain in the quadrivalent vaccine.



For the 2017-18 season, interim results show the vaccine lowered the number of cases of medically attended flu illness by 36 percent. Vaccine effectiveness against influenza A(H3N2) was 25 percent for all ages and 51 percent for children aged 6 months to 8 years. The vaccine was 67 percent effective against A(H1N1)pdm09, and 42 percent effective against influenza B (mostly B/Yamagata, not in inactivated influenza vaccine, trivalent).

"In terms of last year's vaccine … even though we've had a bad flu year, the strains that were selected … were really good selections," said Jack Bennink, PhD, a temporary voting member on the committee and senior managing epidemiologist at the National Institute of Allergy and Infectious Diseases. "They were as good as one could guess and make at the time. I don't think we could've done any better, and I'm encouraged by the fact that particularly [in children aged 6 months] to 8 years old, it's almost 60 percent effective." ❖

Brown T. FDA Committee Recommends 2018-2019 Influenza Vaccine Strains. Medscape, March 1, 2018. Accessed at www.medscape.com/viewarticle/893314.

Research

Heart Failure Death Risk Drops 50% in Those Who Receive Flu Vaccine

A new study shows people with heart failure who receive a seasonal influenza (flu) vaccine have a 50 percent drop in the risk of death during flu season and a 20 percent drop in the risk of death during the rest of the year. In the meta-analysis, researchers analyzed six studies conducted in the U.S., Europe and Asia that included data for more than 78,000 patients with heart failure. Five of the studies were observational and one was a retrospective analysis of clinical trial results. They found getting the flu vaccine reduced the risk of dying (from any cause) by about half during flu season and by about one-fifth during the rest of the year. Vaccination was also associated with a 22 percent reduction in the risk of being hospitalized for cardiovascular problems.

"It is well-known that influenza infection is associated with increased risk of mortality in heart failure patients," said Hidekatsu Fukuta, MD, a cardiologist at Nagoya City University Graduate School of Medical Sciences in Nagoya, Japan, and the study's lead author. "Given the high mortality rate and the relative low influenza vaccination rates in heart failure patients worldwide, our study supports a wider use of influenza vaccination in heart failure patients."

The study's authors caution, however, that while observational studies can show associations, they do not necessarily prove cause and effect. Therefore, said Dr. Fukuta, "Randomized controlled studies should be planned to confirm our observed potential survival benefit of influenza vaccination in these patients." ❖

Getting Influenza Vaccine Linked to 50% Drop in Risk of Death for Heart Failure Patients. News Medical, March 1, 2018. Accessed at www.news-medical.net/news/20180301/Getting-influenza-vaccine-linked-to-5025-drop-in-risk-of-death-for-heart-failure-patients.aspx.

Research

Cell-Based and Recombinant Vaccines More Effective in 2017-18 Flu Season

New data shows cell-based and recombinant vaccines were more effective in the 2017-18 influenza (flu) season, according to U.S. Food and Drug Administration (FDA) commissioner Scott Gottlieb, MD. "The data aren't final yet, but I'm comfortable saying that I think it's going to be about 20 percent improved efficacy for the cell-based vaccine relative to the egg-based vaccines," said Dr. Gottlieb. "As we consider greater investment in alternative vaccine development processes, it's important to note, however, that there are also challenges with these newer cell-based approaches. To help address these challenges, the FDA is working to help develop more effective cell lines that can be better scaled through continuous manufacturing. We're also looking at how we develop a more robust recombinant vaccine manufacturing process to increase yield while reducing cost." ❖

Keet E. FDA Says Cell-Based Flu Vaccine May Be 20% More Effective Than Egg-Based Vaccine. Contagion Live, March 28, 2018. Accessed at www.contagionlive.com/news/fda-says-cell-based-flu-vaccine-may-be-20-more-effective-than-egg-based-vaccine.

Vaccines

CDC OKs FluMist for 2018-19 Influenza Season

The Centers for Disease Control and Prevention's advisory committee has voted 12-2 to recommend FluMist, the nasal spray version of the influenza vaccine, be used during the 2018-19 influenza (flu) season. FluMist is a live attenuated influenza vaccine licensed for use in otherwise healthy, nonpregnant people ages 2 years through 49 years. For the past two flu seasons, FluMist has not been recommended because of poor performance compared with the flu vaccine.

The decision was based on data from AstraZeneca, manufacturer of FluMist, that addressed a possible root cause of poor effectiveness against the influenza AH1N1 virus and a potential solution to address it, which includes using a different type of influenza AH1N1 virus in the vaccine. Specifically, AstraZeneca presented positive results from a U.S. study in children ages 2 years to 4 years that evaluated their responses to the H1N1 strain in the quadrivalent formula of the spray, which protects against four different influenza viruses. Results showed the H1N1 strain in the 2017-18 vaccine performed significantly better than the H1N1 strain in the 2015-16 vaccine.

Even though FluMist has not been recommended for the past two flu seasons, the U.S. Food and Drug Administration (FDA) has still approved it. The availability of FluMist in the U.S. for the 2018-19 influenza season is pending annual strain approval from FDA. ❖

Scutti S. FluMist Set to Return for Next Flu Season. CNN, Feb. 21, 2018. Accessed at www.cnn.com/2018/02/21/health/flumist-returns-cdc-bn/index.html.

Research

Study Finds Asthma Treatments for Kids More Likely to Fail Without Flu Shot

New research shows an annual influenza (flu) shot is crucial for children with asthma. In the study, researchers examined approximately 1,000 children treated for moderate or severe asthma attacks in emergency rooms at five Canadian hospitals. In addition, they analyzed nose swabs taken from those kids to determine if they also had the flu or another respiratory virus. Of the nearly two-thirds tested positive for a viral infection, 19 percent who were given the standard treatments for an asthma attack (including oral corticosteroids and inhaled bronchodilators) didn't respond to their medications. They found that those with influenza or parainflunza had a 37 percent higher chance of not responding to asthma treatments compared to 13 percent without the virus. Asthma treatments were also more likely to fail among children with respiratory sincytial virus. However, human rhinoviruses (the usual cause of common colds) did not reduce the effectiveness of asthma treatments.

According to Francine Ducharme, MD, a pediatrician and co-author of the study, "We now know that if these kids get the flu, the risks are very high that emergency treatment for an asthma attack will fail. Instead of having an 18 percent risk of treatment failure, with flu, the risk rises to 40 percent. These kids should get their flu shot and they should get it systemically; it's worth it."

The study was published in the June 4 issue of *Pediatrics*. ❖

Dallas ME. Kids with Asthma Need a Flu Shot: Study. WebMD, June 4, 2018. Accessed at www.webmd.com/asthma/news/20180604/kids-with-asthma-need-a-flu-shot-study.

Research

Mumps Vaccine Protection Wanes Over Time, According to Meta-Analysis

A recent meta-analysis of six studies of mumps vaccine effectiveness conducted in the U.S. found protection against mumps lasts an average of 27 years after the last dose of the vaccine. In addition, researchers estimated 25 percent of Americans who were vaccinated against mumps as children may lose protection within about eight years, 50 percent within 19 years and 75 percent within 38 years. They also found weakening immunity to mumps played a major role in the recent reemergence of mumps among young adults. The findings suggest that in addition to the recommended two doses of mumps vaccine in childhood, adding a third dose or booster shot at age 18 could help maintain protection. ❖

Mumps Vaccine Protection May Be Waning, Driving Rise in U.S. Cases. United Press International, March 21, 2018. Accessed at www.upi.com/Health_News/2018/03/21/Mumps-vaccine-protection-may-be-waning-driving-rise-in-US-cases/2411521663206.

Vaccines

Researchers Find Vaccines Don't Weaken Babies' Immune Systems

In response to concerns from parents about whether multiple vaccines in early childhood could weaken their children's immune system, researchers conducted a study that examined whether the vaccine schedule was associated with an increased risk of infections not targeted by vaccines (referred to as "nontargeted infections"). They found no statistically significant differences in estimated cumulative vaccine antigen exposure through the first 23 months of life.

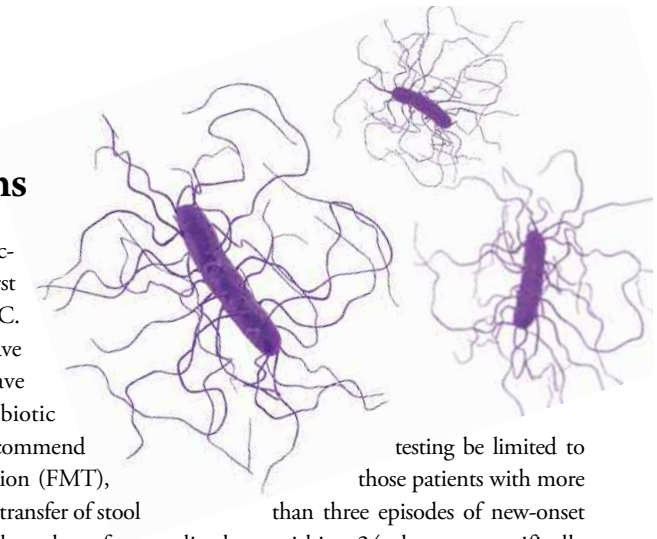
The nested case-control study examined 193 children with nonvaccine-targeted infections and 751 controls without nonvaccine-targeted infections in six U.S. healthcare organizations participating in the Vaccine Safety Datalink. Participants were children ages 24 months through 47 months born between Jan. 1, 2003, and Sept. 31, 2013, who were followed until Dec. 31, 2015. Cases of nonvaccine-targeted infection were matched to controls by age, sex, healthcare organization site and chronic disease status. Cumulative vaccine antigen exposure was estimated by adding the number of antigens in each vaccine dose received from birth through age 23 months.

Among the 944 participants (mean age 32.5 months; 45 percent female), the estimated mean cumulative vaccine antigen exposure was 240.6 for cases and 242.9 for controls, with a between-group difference for estimated cumulative antigen exposure -2.3. The researchers concluded that "among children from 24 through 47 months of age with emergency department and inpatient visits for infectious disease not targeted by vaccines, compared with children without such visits, there was no significant difference in estimated cumulative vaccine antigen exposure through the first 23 months of life." ❖

Glanz JM, Newcomer SR, Daley MF, et al. Association Between Estimated Cumulative Vaccine Antigen Exposure Through the First 23 Months of Life and Non-Vaccine-Targeted Infections From 24 Through 47 Months of Age. *JAMA*, 2018;319(9):906-913. Accessed at jamanetwork.com/journals/jama/article-abstract/2673970?redirect=true.

Guidelines

Updated C. Diff Guidelines Reflect New Treatment Options and Recommendations



The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) have updated guidelines for diagnosis and management of Clostridium difficile (C. diff), which has become the leading cause of diarrhea in hospital patients and one of the most common healthcare-associated infections that sickens nearly 500,000 Americans and is associated with 15,000 to 30,000 deaths annually. The last IDSA/SHEA guidelines for C. diff were issued in 2010. And, while many of the recommendations remain the same, the updated guidelines reflect new treatment options and recommendations for who should be tested and which diagnostic tests are most appropriate.

The previous guidelines recommended metronidazole as first-line therapy for initial cases of mild-to-moderate C. diff and vancomycin for more severe cases. But, the updated guidelines recommend either vancomycin or fidaxomicin as the drug of choice for all initial episodes based on high-quality evidence that both drugs are superior to metronidazole. They also recommend both drugs for a first and second recurrence of C. diff. But, for patients who have had several bouts and have failed all appropriate antibiotic treatments, the guidelines recommend fecal microbiota transplantation (FMT), a procedure that involves the transfer of stool from a healthy donor into the colon of an infected patient. FMT is still considered an investigational treatment by the U.S. Food and Drug Administration, but it has produced strong results in anecdotal reports and in randomized clinical trials. "An important aspect of susceptibility to C. difficile, if not the majority of susceptibility, is due to disruption of the microbiota by antibiotics," said Clifford McDonald, MD, senior advisor with the Centers for Disease Control and Prevention. "These patients can have multiple recurrent C. diff, they're failing over and over again, and that's where FMT is now another tool in the toolbox."

The new guidelines also recommend testing be limited to those patients with more than three episodes of new-onset diarrhea within 24 hours, specifically patients whose symptoms aren't attributable to underlying conditions or use of laxatives. In addition, it is recommended molecular tests, which have become increasingly popular in recent years due to their high sensitivity and quick diagnosis, be used on their own only when hospitals have established criteria for patients who are most likely to be at risk for C. diff. When the criteria don't exist, a two- to three-step process that includes a toxin immunoassay plus a molecular test and/or an antigen test are recommended. ❖

Dall C. New C Diff Guidelines Incorporate Fecal Transplant. Center for Infectious Disease Research and Policy, Feb. 16, 2018. Accessed at www.cidrap.umn.edu/news-perspective/2018/02/new-c-diff-guidelines-incorporate-fecal-transplant.

Guidelines

Zika Virus Blood Screening Guidelines Revised by FDA

The U.S. Food and Drug Administration (FDA) has revised its recommendations for testing blood donations for the Zika virus, allowing for pooled testing of donations using a screening test it has licensed. The revised guidance replaces guidance announced in August 2016 that recommended universal nucleic acid testing for Zika virus of individual units of blood donated in U.S. states and territories. Roche's cobas Zika test for use on the cobas 6800 and 8800 PCR systems enables streamlined screening of multiple individual blood or plasma donations that have been pooled together. The test is a qualitative in vitro nucleic acid screening test for the direct detection of Zika virus DNA in

plasma specimens from individual human blood donors. According to Peter Marks, director of FDA's Center for Biologics Evaluation and Research, the new approach is usually more cost-effective and less burdensome for blood establishments.

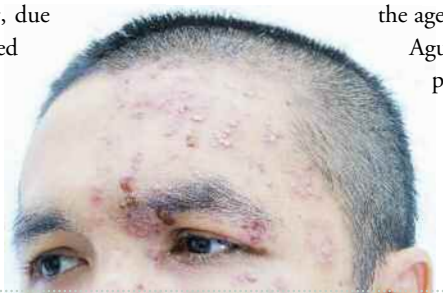
"When Zika virus first emerged, the unknown course of the epidemic and the observed severe effects from the disease indicated that individual donor testing was needed to ensure the continued safety of the blood supply," explained Marks. "Now, given the significant decrease in cases of Zika virus infection in the U.S. and its territories, we are moving away from testing each individual donation to testing pooled donations. [However, FDA] will continue to monitor the situation closely, and as appropriate, reconsider what measures are needed to maintain the safety of the blood supply." ❖

FDA Revises Zika Virus Screen Guidance, Recommends Pooled Testing of Blood. Genomeweb, July 6, 2018. Accessed at www.genomeweb.com/regulatory-news/fda-revises-zika-virus-screening-guidance-recommends-pooled-testing-blood#.W0SuniOZM1g.

Medicines

CDC Expects Shortage of New Shingles Vaccines

The Centers for Disease Control and Prevention (CDC) is warning about a shortage of Shringrix, the newest shingles vaccine recommended for individuals 50 years and older, due to greater-than-expected demand. "It's a really potent, excellent vaccine. I got it myself. And this is a vaccine where the old vaccine worked 30, 40 percent of the time. This is 97 percent of the time. And, remember, over a third of the population will get shingles, so this is something for everybody over the age of 50," said David Agus, MD. "Even people who have the old vaccine need to get the new vaccine."



Shingles is triggered by the chicken pox virus and causes a painful blistering rash along with possible complications, including searing nerve pain and pneumonia. Individuals are encouraged to get on the list to receive it. "Every week, [the company is] releasing more of [the vaccine], so get on the list. Figure out where it is. It's not a critical shortage, but it's a shortage," said Dr. Agus. ❖

CDC Warns of Shingles Vaccine Shortage. CBS News, June 29, 2018. Accessed at www.cbsnews.com/news/cdc-warns-of-shingles-vaccine-shortage-shingrix.

Medicines

FDA Approves First Treatment for High-Risk Prostate Cancer

The U.S. Food and Drug Administration (FDA) has approved Erleada (apalutamide) to treat men with prostate cancer that has not yet spread but has a quickly rising PSA level while on treatment with hormone therapy, which causes concern for cancer growth and spread. This is the first FDA-approved treatment for this high-risk type of prostate cancer known as nonmetastatic castration-resistant prostate cancer. Erleada works by blocking the effects of androgens, a type of hormone, on the tumor. Androgens such as testosterone can help tumors grow.

Approval under FDA's priority review program was based on a randomized clinical trial of 1,207 men with high-risk nonmetastatic castration-resistant prostate cancer that measured the amount of time patients' tumors did not spread (metastasize). All men in the trial received hormone therapy, but only some also received Erleada. Those who received Erleada had no metastasis for an average 40.5 months compared to 16.2 months for men who did not receive the drug. ❖

FDA Approves Erleada (Apalutamide) for Some Prostate Cancers. American Cancer Society, Feb. 15, 2018. Accessed at www.cancer.org/latest-news/fda-approves-erleada-apalutamide-for-some-prostate-cancers.html.

Research

Current Pertussis Vaccine Mounts a Weaker Recall Response with Booster Shots

Researchers at the La Jolla Institute for Allergy and Immunology have found individuals who had been inoculated with the newer pertussis (whooping cough) vaccine as part of their initial series of shots mount a weaker recall response when receiving booster shots later on. Specifically, the study found the new vaccine, which replaced the original vaccine in 1996, fell short of generating a robust T cell response, which provides the long-term memory that allows the immune system to mount a rapid response if exposed to the pathogen. "Ideally, you should engage both arms of a protective response against pathogens — B cells that produce antibodies and T cells that generate long-term memory," said Ricardo Antunes, PhD, a postdoctoral researcher and first author of the study. "But, apparently, the new vaccine fails to generate an adequate T cell response. Although B cells are a very important component of vaccine efficacy, the important role of T cells is being more and more appreciated and the key point of our study is to show that there are striking differences in the T-cell response to the two different vaccines."

In the study, researchers recruited 114 healthy adults who had been originally vaccinated with the whole pertussis (wP) vaccine (the original vaccine crafted from dead bacteria that came with unwanted side effects) or the acellular pertussis (aP) vaccine (the new vaccine that relies on purified bacterial proteins to induce immunity) in infancy and administered booster vaccinations with aP in middle and high school and as adults, and analyzed their immune response at regular intervals. Their results showed that priming in the first few months after birth with the aP or wP vaccines induces different T-cell responses. And, while both are initially capable of generating protective immunity, differences evolve over more than 15 years. In addition, T cells originally primed with aP gradually lose the ability to respond to booster vaccination. "These cells just sit there and do nothing while T cells primed with wP respond with a pronounced boost," said Dr. Antunes.

The study was conducted because the birth years of the teenagers and young adults most affected by the sudden increase in pertussis cases coincided with the nationwide switch from the wP to the aP vaccine. According to the researchers, unraveling the differences between the two vaccines is key to understanding how to better prevent whooping cough and may also provide important lessons on vaccine efficacy in general. ❖

Whooping Cough Vaccine: The Power of First Impressions. La Jolla Institute for Allergy and Immunology, July 9, 2018. Accessed at www.sciencedaily.com/releases/2018/07/180709143912.htm.

Research

Immune System Response Discovery in Newborns Could Lead to Earlier Vaccine Administration

Researchers at the TCD School of Medicine and the National Children's Research Centre (NCRC) in Ireland have discovered a distinct immune response in newborns that could lead to both earlier vaccine administration and reduced need for multiple booster shots. According to the researchers, their discovery is a "class of danger signals" that are highly efficient at triggering an immune response in young infants.

The discovery was made after scientists theorized newborns may retain a more robust immune response to viruses and found a class of adjuvants (one of two key components in vaccines) that activate specialized sensors that drove a very strong immune response in newborns where other microbial infections arise. "These sensors are normally activated in response to viral infection and direct the immune system to clear up viral infections," said Sarah Doyle, MD, of the NCRC. "Harnessing these efficient antiviral immune responses will help in the design of targeted adjuvants for pediatric vaccines by directly activating immune responses that are fully functional in neonates and infants."

"Many adjuvants used in vaccines today were developed in adults; however, babies and children are not simply little adults, and because of this, a child's immune system responds differently than an adult's immune system does," said Kiva Brennan, MD, at TCD School of Medicine and lead author of the study. As a result, the key to improving vaccine efficacy is the design of adjuvants that specifically target and kick the newborn immune response into action." ❖

O'Sullivan K. Irish Scientists Find Distinct Immune System in Newborn Babies. *The Irish Times*, July 16, 2018. Accessed at www.irishtimes.com/news/health/irish-scientists-find-distinct-immune-system-in-newborn-babies-1.3566105.

Guidelines

WHO Recommends Typhoid Vaccine in Children in Endemic Countries

The World Health Organization (WHO) is recommending a single dose of the typhoid conjugate vaccine (Typbar-TCV) for use in infants and children older than 6 months and a catch-up vaccine in children up to 15 years in countries where the infection is endemic. The recommendation is a result of a review of the vaccine by WHO's Strategic Advisory Group of Experts on Immunization in October 2017 that considered data on vaccine safety, efficacy, feasibility and affordability, as well as growing rates of drug-resistant typhoid. The Typbar-TCV vaccine provides longer-lasting protection and fewer doses than previous vaccines.

"Studies have shown that TCV is safe, effective and can provide protection for infants and children under 2 years of age, unlike the previous available typhoid vaccines," said Adwoa Bentsi-Enchill, MD, medical officer of the Department of Immunization, Vaccines and Biologicals at WHO. "The recommendation for the typhoid conjugate vaccine to be included in routine immunization programs will help pave the way for national authorities to introduce this vaccine in countries where they are needed most." ❖

First Typhoid Conjugate Vaccine Recommended by WHO. Contagion Live, April 3, 2018. Accessed at www.contagionlive.com/news/first-typhoid-conjugate-vaccine-recommended-by-who.

Research

Tuberculosis Vaccine May Reverse Type 1 Diabetes

A recent study shows two injections of the bacillus Calmette-Guérin (BCG) vaccine (used to prevent tuberculosis) a few weeks apart may reverse the causes of type 1 diabetes over several years. In the study of 52 participants, nine received the injections and three received a placebo. Those who received the injections had a substantial reduction in the blood-sugar marker HbA1c used to diagnose diabetes: a 10 percent reduction after three years and 18 percent after four years, bringing them below the cutoff point for a clinical diagnosis. And, after being followed for an additional eight years, most retained the reduction. In contrast, those who received a placebo and followed normal diabetic management saw their blood sugar measurement rise by a few percentage points during the same periods. All study participants continued to use insulin during the study period.

"Nobody thought you could intervene with an immunotherapy in people 10, 20 years out," said the study's principal director Denise Faustman, MD, director of the Massachusetts General Hospital Immunobiology Laboratory. "To have data showing durability for eight years, without revaccination, is remarkable." ❖

Fleishman G. Tuberculosis Vaccine Could Reverse Type 1 Diabetes, Study Shows. *Fortune*, June 21, 2018. Accessed at fortune.com/2018/06/21/tuberculosis-vaccine-reverse-juvenile-diabetes-study-shows.

Artificial Intelligence and Big Data

A CROSSROADS OF INTEROPERABILITY AND CAPABILITY

Touted as the future of medicine, AI also has many ethical unknowns that will require discussion apace with progress.

By Amy Scanlin, MS

ON APRIL 11, the U.S. Food and Drug Administration (FDA) approved the first medical device for use as part of an artificial intelligence (AI) algorithm, further solidifying the expanding role of AI's use in the medical community. By some estimates, AI growth in healthcare is expected to increase by 40 percent per year to reach $6.6 billion in 2021,[1] and AI technologies could overtake human performance in surgeries by 2053.[2] This could amount to an annual savings of over $1 billion for the healthcare industry.[3]

While touted as a revolution and the future of medicine, AI is at the same time feared for its potential unknowns. How will it threaten healthcare as we know it? Will it take over jobs, making more mundane tasks obsolete? Will it render diagnoses with increasingly greater accuracy — perhaps even more so than those made by humans? Is there a risk to good governance as the potential for innovation reaches new technological boundaries?

AI has the potential to provide patients a wealth of expertise beyond the walls of their doctor offices, and it offers providers an opportunity to put more personal time back into patient care. It is gaining momentum in reading common language medical records, looking for supporting information that can answer any number of questions. It is successfully being used in diagnostics such as assessing the likelihood of cancers through photos and MRIs. And, it can scan for contraindications and support the development of personalized medicine. AI's potential is unending, but at what cost? Cautionary histories, such as those of AI's use in the early days of genetics studies, remind us that although AI is expanding rapidly, ethical considerations must always be kept at the forefront.

AI in Diagnostics: "Deep Learning"

What if a radiology report could be interpreted accurately in the blink of an eye? Incredibly, AI is teaching itself to do just that via "deep learning." Deep learning goes well beyond "if then" scenarios, although exactly how it does so is still largely a mystery. It uses AI black boxes that look at tens of thousands of scanned images, such as melanoma, abnormal EKGs and blood clots, to learn what they do and don't look like, and they are learning to do this with increasing sensitivity. In fact, researchers feeding images into this learning tool must remove extraneous blips or annotations, such as circles and arrows pointing to anomalies, so as the machine scans and learns the images, it doesn't associate those blips with the anomalies themselves.[4]

The black box part of the equation means the machine is teaching itself to learn in a manner akin to how brains learn, strengthening its electronic synapsis through repetition. Much like as children we begin to recognize a dog from a cat and a horse from a cow, these machines also develop sensitivities to help them discern. Through scanning, calculating and then recalculating as new images are fed into the system, the machines generate new and improved outputs. When an output is incorrect, such as in a case of a patient who does eventually develop cancer, a correction can be fed back into the machine so it can learn again as it continues to improve.

The results are impressive. In one example, researchers at Stanford fed 14,000 master images of various types of diagnosed skin cancers and abnormal growths into a system. Their 2015 tests of new images against validation tests found their machine, which provided results in probabilities, was correct 72 percent of the time, beating two board-certified dermatologists who, when assessing the same new images, were accurate only 66 percent of the time. Further, an expanded test with 25 board-certified dermatologists produced similar results, with the machine showing an overall greater sensitivity and specificity.[4] Even more impressive, an industry competition in which assessments were made with the combined skills of AI *and* humans saw a reduction in errors of breast cancer detection by 85 percent.[1]

While touted as a revolution and the future of medicine, AI is at the same time feared for its potential unknowns.

But what about AI's challenges? In addition to the many serious HIPAA implications, one very big concern is how far to ethically go, particularly in the case of AI versus human. If we remove the human factor, would there be an increased risk, due to the incredible sensitivities, for unnecessary biopsies, particularly in those cases where the identified lesion may be less aggressive? Or, as others would argue, is any early diagnosis worth that risk? If machines have the capability to improve outcomes, should they be allowed to?

Many who study AI, however, do not fear the inevitability of machines taking over healthcare. Instead, they see technology as augmenting it, with the machine doing more of the "yes/no" diagnoses, allowing for a more evolving role of increasingly involved caregivers who have more available time to spend with patients. After all, patients feel better about their care when they have meaningful interactions with their providers, learning not just the "whats" but, equally important, the "whys." While

machines may someday be able to provide the "what" in an office prescreen, they can't ask questions and they can't determine the "why." Perhaps, then, by using AI as an enhancement to medicine, physicians may be better able to spend more time looking for a root cause, in addition to discussing treatment options and providing their patients better peace of mind.

AI and the Data Mine: "Deep Patient"

As we continue to feed data into these machine aggregators, the ability to scan medical records, search vast amounts of medical literature (estimated to grow by 8,000 academic articles published daily[5]), assess images, formulate predictions and extrapolate data from personal devices is also gaining ground. With so much information to sift through, finding meaningful connections far outweighs our traditional analytical capabilities. After all, as more and more data pours in, how do we extract meaningful information?

While machines may someday be able to provide the "what" in an office prescreen, they can't ask questions and they can't determine the "why."

AI can sift through huge quantities of information in rapid time. It can find linkages and trends, and it eliminates the need to discard data that might otherwise be assumed irrelevant or just too vast to include in the equation. AI can provide a more complete picture of health and health history (even familial history) and develop a better roadmap to care. Dubbed "deep patient," early studies are showing machines can connect data humans may not be able to easily see. Machines aren't looking at any one thing; they are looking at everything. By combining de-identified hospital data with other inputs, without any specific limiting parameters, AI avoids zeroing in on any one thing at the exclusion of others.[1] Information is combined in unique ways to build a comprehensive picture — a predictive model — and helps humans make decisions.

As data becomes less and less expensive to collect and store, and computer processing capabilities become faster, cheaper and more precise, data provides the opportunity to gather and sort information from increasingly expanding sources. It can lower healthcare costs, improve outcomes, save time and potentially eliminate unnecessary tests and treatments. It can drive the economic machine that has become healthcare as it satisfies demands for improved results. It also has the potential to lower the risk and impact of medical insurance fraud.

But, AI has a huge limitation: interoperability challenges. A lack of common language between many of the systems has led to an inability to achieve true connectivity. Our medical records, devices and more, at least today, don't easily speak to one another. As much as AI has the potential, it is also limited by siloed systems keeping information boxed into their current configurations. The Affordable Care Act is attempting to encourage inroads through its meaningful use incentives, but for AI, there is still a long way to go.

Currently, FDA is actively developing a new regulatory framework to promote innovation in the AI space and to support AI-based technologies — even within a system in which trusted entities are precertified as innovators without requiring additional submissions for each successive minor improvement. This is a real regulatory challenge, particularly in the area of machine learning. How does the agency regulate something when even its designers don't fully understand how it works?

Genetics and Genomics

As capabilities and ethical considerations abound, AI's resurgence in the field of genetics is both an opportunity and a challenge. The question is: Even though we can alter some of our 20,000-some genes, providing new instructions to build, repair or maintain status quo, should we? Machines can assess a patient's specific tumor, genetic mutations and available drugs to determine a pathway forward with the greatest chance for success. That sounds good, but what is the subjective definition of success? Could subjective definitions and subsequent treatments that have the potential to eliminate a disease be too far-reaching for man to decide?

This question is very pertinent to the study of genomics, particularly germline cells. It is conceivable science could evolve to where genes could be altered for creation of a "healthier" individual. That raises concerns about man's ability to control destiny and whether a certain condition should be eliminated just because we have the capability. In some circles, the answer is yes, but only for the most devastating conditions that cause immense suffering or are incompatible with life. However, how the criteria are defined is another question, as is the subjectiveness of the definition. Currently, heritable germline therapy is illegal in the U.S., and a number of other countries have signed an agreement prohibiting germline modification.[6]

The American Society of Human Genetics board adopted a position stating it is inappropriate to conduct germline therapy that culminates in human pregnancy. However, it also stated if there is appropriate oversight and consent, it is acceptable to edit in vitro germline genomes of human embryos for the benefit of scientific study. In addition, its position states any "future clinical application of human germline genome editing should not proceed unless, at a minimum, there is a) a compelling medical rationale, b) an evidence base that supports its clinical use, c) an ethical justification and d) a transparent public process to solicit and incorporate stakeholder input."[7]

Siddhartha Mukherjee reminds us in his book *The Gene — An Intimate History* that genes are recipes, not blueprints. What this means is even in cases in which a gene could be permanently altered, the end result cannot be predictably known due to determinants such as environmental and behavioral triggers, and even chance. The challenge becomes exponentially harder when considering combination gene variants in which outcomes are governed by multiple genes.[8]

Still, studies progress, particularly with the use of the CRISPR-Cas9, a technology adapted to function similarly to that of a human genome. In humans, bacteria capture snippets of DNA from invading viruses and use them to create DNA segments known as CRISPR arrays. These CRISPR arrays allow the bacteria to "remember" the viruses (or closely related ones) so that if the viruses attack again, the bacteria produce RNA segments from the CRISPR arrays to target the viruses' DNA. The bacteria then use Cas9 (or a similar enzyme) to cut the DNA apart, disabling the virus. In the laboratory, it works much the same way, and the eventual result is the cell's own DNA repair machinery adds or deletes pieces of genetic material, or makes changes to the DNA by replacing an existing segment with a customized DNA sequence. Research using CRISPR-Cas9 technology in humans has only just gotten underway in the West for a wide variety of diseases, including single-gene disorders such as cystic fibrosis, hemophilia and sickle cell disease. It also holds promise for the treatment and prevention of more complex diseases such as cancer, heart disease, mental illness and HIV.[9]

One area of agreement on the potential for genomic editing is the need for more discussion about its scientific potential and future opportunities and utility, as well as the ethical question of how far this line of study should be pursued. The National Academies of Sciences, Engineering and Medicine's (NASEM) Human Gene-Editing Initiative, while firm in its position that safety, technical and ethical issues bar a wide application of germline therapy studies beyond treatment of disease or disability, does encourage additional discussion on the topic. NASEM recommends strict conditions for the study of germline therapy as part of its 2017 report "Human Genome Editing: Science, Ethics and Governance."[10]

A Need for Intelligent Discussion

While there are many questions and much debate about how AI should move forward for the enhancement of medical care, there is no question the rapid pace of progress requires an ongoing discussion to happen simultaneously. How will AI be integrated into medical care? Is it possible to unintentionally insert bias into decision-making algorithms? What are the legal ramifications when a prediction is wrong, and how will FDA regulate this rapidly changing technology?

As capabilities and ethical considerations abound, AI's resurgence in the field of genetics is both an opportunity and a challenge.

More and more data is available to us every day, although it is fractured and, in some cases, unusable in its current state. The future capabilities of capturing, storing, translating and analyzing data to provide meaningful information for the improvement of patient care is at the root of AI's interoperability. AI is here to stay, and we need to be intelligent about how its growth is nurtured and used. ❖

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The Future of Cord Blood

Once thought to be a useless byproduct, umbilical cord blood is being used to treat more than 80 diseases today, and research indicates, in the future, it may be used to treat conditions far beyond just those that affect the blood and immune systems.

By Ronale Tucker Rhodes, MS

A ONCE-DISCARDED birth byproduct, umbilical cord blood (UCB) has the potential to save thousands of lives each year in the U.S. For people born with life-threatening blood and immune system diseases, the best treatment is a bone marrow or blood cell transplantation from a related or unrelated donor or cord blood unit.[1] Until recently, bone marrow transplantation has been the standard, as not much thought was given to UCB.

Beginning in the 1980s, doctors proposed it might be useful for treating some diseases. It was then that scientists realized UCB contained blood (haematopoietic) stem cells (HSCs), which can produce all other cells found in blood, including red blood cells, white blood cells and platelets. It is now known HSCs are responsible for maintaining blood production throughout life.[2,3]

Today, more than 20 years after the first successful UCB stem cell transplant, cord blood is changing lives with 13 percent of transplant patients receiving UCB donated to public cord blood banks.[3,4] But, uses of cord blood are still in the beginning stages, and researchers believe this substance could radically transform medical strategies over the next few decades.

Harvesting Cord Blood

The closed technique is the most common method of harvesting cord blood stem cells, and it poses no risk to the mother or baby. This method is similar to drawing blood from a person. After a baby is born, cord blood is left in the umbilical cord and placenta, and then extracted by inserting a needle into the umbilical vein on the part of the cord that is still connected to the placenta. The typical amount removed is one to five ounces, and it takes less than 10 minutes to perform.[2,5]

Historically in Western countries, the umbilical cord was clamped and cut between 10 seconds and 15 seconds after birth. Now, more health organizations are recommending waiting for a period of time to clamp and cut a newborn's umbilical cord after birth,[6] thus decreasing the amount of cord blood that can be collected. These recommendations correlate with the World Health Organization's (WHO) recommendation in 2012 that the umbilical cord should not be clamped earlier than necessary. Specifically, WHO recommends late cord clamping (performed approximately one to three minutes after birth) for all births.[7]

Recent research shows delayed cord clamping can benefit the newborn by allowing more blood to move from the placenta into the newborn, thereby increasing the child's iron and hemoglobin levels and reducing the risk of iron deficiency during infancy, without increased risk to the mother. But, that means less blood is left in the umbilical cord, raising the question of whether there is enough cord blood to harvest. Fortunately, only approximately 50 mL of blood is necessary for cord blood storage, which is just a portion of the approximately 200 mL of blood contained in the placenta and umbilical cord. So, if cord clamping is delayed by

one minute, about 80 mL of this blood is transferred into the infant, leaving more than enough to be stored in a cord blood bank. And, even if clamping is delayed by three minutes, only approximately 100 mL will have gone into the baby.[8] Thus, such delayed clamping and cord blood collection are compatible.

Current Uses of Cord Blood

Cord blood is approved by the U.S. Food and Drug Administration (FDA) only for use in hematopoietic stem cell transplantation (HSCT) procedures, which are performed in patients with disorders affecting the hematopoietic (blood forming) system.[9] To date, HSCT using cord blood has treated more than 80 different diseases. The most commonly treated disease category is leukemia, followed by inherited diseases of red blood cells, the immune system, metabolic abnormalities and others (Table 1).[10] "Cord blood is useful because it is a source of stem cells that form into blood cells," explains Keith Wonnacott, PhD, chief of the cellular therapies branch in FDA's Office of Cellular, Tissue and Gene Therapies. "Cord blood can be used for transplantation in people who need regeneration, that is, 'regrowth,' of these blood-forming cells."[9]

Today, more than 20 years after the first successful UCB stem cell transplant, cord blood is changing lives with 13 percent of transplant patients receiving UCB donated to public cord blood banks.

Cord blood can be used to treat the child from whom it was harvested, or to treat that child's first- or second-degree relatives when it is stored in private cord banks. And, it can be used to treat individuals unrelated to the child after it has been donated to a public cord blood bank.[9]

Advantages and Limitations

There are a number of advantages to cord blood transplantation over bone marrow transplantation. For one, it is easy to collect. And, since it is donated in advance, routine testing is complete, and if a match is found, it can be reserved immediately with confirmatory human leukocyte antigen (HLA) typing and any special testing usually completed in five days. Therefore, unlike bone marrow, there is no need to take time to locate a possible volunteer to see if he or she is willing to donate.[11]

A significant advance is that studies have shown cord blood transplants can be performed even when the donor and recipient are partially matched, whereas bone marrow transplants require a perfect match in most cases. As such, a relatively small cord blood donor pool can support most patients' needs. For example, the New York Blood Center's National Cord Blood Program (NCBP) estimates a national inventory of 150,000 cord blood units would provide acceptable matches for at least 80 percent to 90 percent of U.S. patients.[11]

What's more, the immune cells in cord blood are less likely than those in bone marrow from unrelated donors to cause graft versus host disease, which occurs when the transplanted cells attack the patient's own tissues. In addition, cord blood is less likely to transmit infectious diseases such as Epstein-Barr virus and cytomegalovirus (CMV) that can be potentially lethal for transplant recipients. In fact, CMV is carried as a latent virus by approximately half of the population, whereas less than 1 percent of infants are born with CMV.[11]

For ethnic minorities, cord blood is particularly important. Because there are differences in the frequency of HLA types among ethnic groups, patients have a much more difficult time finding an unrelated bone marrow donor. The problem is simply numerical since minority groups have smaller numbers from which to draw potential donors. This is particularly true of African-Americans who make up only 12 percent of the U.S. population. In fact, epidemiological estimates indicate at least three times as many African-American volunteer bone marrow donors than Caucasian donors would be needed for African-American patients to have a chance that equals that of Caucasian patients to find a match in the same bone marrow donor registries. The same problem is true for many Hispanic and Asian patients, who tend to have ancestors from more than one ethnic group. At the NCBP, 54 percent of U.S. patients transplanted have been non-Caucasian, 16 percent of whom have been African-Americans.[12] And, at the Be The Match Registry, a listing of potential marrow donors and donated cord blood units, 28 percent of cord blood transplants in 2017 were for patients of color.[4]

Worth noting, a disadvantage of cord blood is that while it is a rich source of HSCs, the volume collected in one cord blood unit is fixed and relatively small, which means it contains fewer HSCs than a customizable bone marrow donation. For instance, the average total nucleated cell dose (number of nucleated cells per kilogram of a patient's weight) in a cord blood graft is less than about one-tenth that of the average bone marrow graft.[13] Because adults are larger and need more HSCs than children, a transplant

containing too few HSCs may fail or could lead to slow formation of new blood in the body in the early days after transplantation. Thankfully, clinical trial results have shown double cord blood transplants (from two different donors) to be very successful.

Additionally, researchers have tried to increase the total number of HSCs obtained from each umbilical cord by collecting additional blood from the placenta. They are also studying ways to expand the number of HSCs from cord blood in labs so a single cord blood donation could supply enough cells for one or more HSC transplants. Known as ex-vivo expansion, this process has shown mixed results in many preliminary clinical trials. Some suggest ex-vivo expansion reduces the length of time for new blood cells to appear in the body after transplantation, but adult patients still need blood from two umbilical cords.[14]

Further limitations of cord blood must be considered, including that not all information about diseases carried in the infant's blood is available as some genetic diseases may not be apparent in the child for months or years, and will not be found or even suspected by current screening methods. Also, cord blood from a newborn infant will not be available for an additional donation of cells, whereas with bone marrow transplants, the donor can be asked to make an additional donation.[13]

Banking on Cord Blood

While cord blood banks are essential to increasing patient access to transplant, the method in which cord blood is stored can be controversial. As mentioned previously, there are two main methods of storage — public and private — as well as a third known as hybrid. Public cord blood banks store cord blood donations for public use free of charge. Private cord blood banks store cord blood units for private use by individual families for a fee. And, hybrid cord blood banks offer both public and private cord blood banking services. According to BioInformant, a stem cell market research firm, as of May 2018, there are 53 cord blood banks in the U.S.: 27 private, 23 public and three hybrid.[15]

Public cord banks make donations available to anyone who needs them. In addition, the banks may use the donated cord blood for research. Patients who wish to donate cord blood to a public bank must talk with their doctor and then make arrangements with a cord blood bank. Because public banks pay for everything, including collecting, testing and storing UCB, cord blood donation is not possible in every hospital. In participating hospitals, the blood left in the umbilical cord and placenta is collected and tested. Cord blood that meets standards for transplant is stored at the public bank until needed by a patient. (It is not saved for the family making the donation.) After the cord blood unit arrives at the public bank, it is checked to ensure it has enough blood-forming cells for a transplant. If there are too few cells, it may be used for research to improve the transplant process for future patients, to investigate new therapies using cord blood or discarded. It is also checked to ensure it is free from contamination. Then, the tissue is typed and listed on the registry of the C.W. Bill Young Cell Transplantation Program, also called the Be The Match Registry, which is searchable to find a matching marrow donor or cord blood unit for a transplant patient. Cord blood donations are kept frozen in a liquid nitrogen freezer to be available if the unit is selected as a match for a patient needing a transplant.[16]

For ethnic minorities, cord blood is particularly important.

The U.S. Congress mandates all patients in need of a transplant have access to bone marrow, blood cell and UCB transplants. The C.W. Bill Young Cell Transplantation Program was authorized in December 2005 after enactment of the Stem Cell Therapeutic and Research Act of 2005. That act was then amended by the Stem Cell Therapeutic and Research Reauthorization Act of 2010 and 2015. In fall, 2006 and 2012, Be The Match was awarded key contracts to carry out the work mandated in the C.W. Bill Young Cell Transplantation Program, including the contract to serve as the nation's Cord Blood Coordinating Center. The stem cell act of 2015 helped patients by creating the National Cord Blood Inventory, whose goal is to collect and store an additional 150,000 cord blood units for patients in need of transplant and for research to continue improving the success of transplants. The act also allows for funding for bone marrow and UCB transplantation and research through Be The Match.[17]

At private banks, cord blood cells remain the property of the donor in case the child or a relative is faced with a serious health issue in the future. Collection and processing are the same as at a public bank. Private banks provide the service for a fee that covers the cost of collection and processing, as well as annual storage. There are two forms of payment that affect the cost: The first, determined by the bank, is an initial payment of approximately $1,500 or more, and it covers only the first year. After that, the donor is required to pay approximately $100 or more annually for storage. The second is cheaper, but the donor pays upfront for storage for 20 years.[18]

According to Save the Cord Foundation, hybrid banks are private banks that also operate a public donation program. Hybrid banks help make donations possible regardless of location since many hospitals do not provide access for donations to public banks. Costs for these programs are often covered in part by the

private side of the business. Due to the costs involved in running a public donation program, though, many hybrid banks limit the number of donations they can accept each year.[19]

A Controversial Cure?

While there is little doubt public storage of cord blood is essential to providing patients access to transplants, many medical professionals and researchers question the usefulness of private cord blood storage.[20] The American Academy of Pediatrics (AAP) encourages parents to keep their child's cord blood if a family member has already been diagnosed with a stem-cell-treatable disease, but the chances of a child actually needing his or her stored cord blood stem cells is anywhere between one in 1,000 and one in 200,000, according to studies cited by the American College of Obstetricians and Gynecologists and AAP.[21] Another study at the University of California, San Francisco, found there is a 0.04 percent chance of a baby requiring a transplant of his or her own stored stem cells to treat a disease and a 0.07 percent chance the baby's sibling will require a stem cell transplant from the baby's stored cord blood.[20]

Private banks' marketing materials, on the other hand, often place the odds at one in 2,700. "Researchers are constantly discovering new treatments using stem cells," says Gerald Maass, executive vice president of corporate development for Cryo-Cell, a private bank in Clearwater, Fla. And, another major bank's website claims: "Should cord blood prove successful in treating heart disease, the lifetime probability of being diagnosed with a disease treatable by cord blood will increase from one in 100 to one in two."[21]

Table 1. Uses of Cord Blood in Transplantation

- Leukemias
- Lymphomas
- Myelodysplasias
- Bone marrow failure syndromes
- Hemoglobinopathies
- Immune deficiencies
- Histiocytosis
- Metabolic/storage diseases
- Neutrophil disorders
- Platelet disorders
- Other malignancies
- Systemic lupus
- Congenital erythropoietic porphyria
- Epidermolysis bullosa

Source: National Cord Blood Program List of Diseases. Accessed at www.nationalcordbloodprogram.org/downloads/list_of_diseases.pdf.

But, the opposing argument that questions cord blood stem cells' usefulness for the donor has merits. According to a 2011 study published in the *Journal of Assisted Reproductive Medicine*, "If cord blood from an infant donor has an inherited hematologic, immunologic or genetic disorder, then cord blood may not be used to expect a cure for the same disease in the same recipient. Therefore, families with recognized genetic diseases should be made aware of these issues." This means if a child has leukemia or if he or she is diagnosed with a genetic illness such as an immune deficiency, the genetic mutations that led to that child's disease is in the DNA of his or her cord blood and is, therefore, unusable.[20]

Also, a controversial issue surrounding private banks remains. As mentioned previously, few cord blood transplants are given to adults because most units don't contain enough stem cells to treat anyone weighing more than 90 pounds, according to Joanne Kurtzberg, MD, program director of the division of pediatric blood and marrow transplantation at Duke University Medical Center. And, says Mary Halet, manager of cord blood operations for the Center for Cord Blood at the National Marrow Donor Program, approximately 75 percent of the units donated to public banks are discarded or used in research because they don't contain enough stem cells for transplants.[21]

Lastly, since the procedure is relatively new, no one knows how many years cord blood can be stored in liquid nitrogen for the cells to remain viable. However, according to NCBP, its earliest units were stored in 1993, and after checking the viability of cells in units that will not be used for transplantation, it has not detected any deterioration in the quality of the cells in those stored for up to 16 years. And, units stored for up to 13 years have been used in transplants, and the outcomes have been similar to those of newly collected units.[22]

Unlocking Cord Blood's Potential

Looking to the future, the use of cord blood stem cells may extend beyond regeneration of healthy blood and immune systems. Several reports suggest cord blood may contain other types of stem cells that can produce specialized cells that do not belong to the blood. To name a few, studies continue on cord blood transplants to treat spinal cord injury, heart attacks, stroke, Alzheimer's, Parkinson's disease, type 1 diabetes, cerebral palsy, traumatic brain injury and acquired hearing loss, among others. Following are highlights from some of these studies:

- In a study published in June 2010, newborn cord blood stem cells improved the neurologic function of rats after an acute spinal cord injury. The rats experienced a significantly improved recovery of locomotor function over a six-week period compared to untreated rats. And, six weeks after treatment, the injured area was noticeably smaller in the treated animals.[23]
- The American Heart Association recently published results of a study that intravenously infused umbilical cord stem cells in 30

patients aged 18 years to 75 years who had stable heart failure. Participants were given the stem cell therapy or a placebo. When analyzing the results, researchers compared the two and noted those who received the stem cell infusion showed sustained and significant fourfold improvement in the hearts' ability to pump blood, reported a greater quality of life and suffered no adverse effects as a result of the therapy.[24]

• In a study assessing the safety and feasibility of a single intravenous infusion of non-HLA-matched, ABO-matched, unrelated allogeneic UCB in adult stroke patients, 10 participants with acute middle cerebral artery ischemic stroke were enrolled. UCB units were matched for blood group antigens and race but not HLA, and infused three to nine days poststroke. The adverse event (AE) profile over a 12-month postinfusion period indicated the treatment was well tolerated with no serious AEs directly related to the study product. Study participants were also assessed using neurological and functional evaluations, including the modified Rankin Score (mRS) and National Institutes of Health Stroke Scale (NIHSS). At three months posttreatment, all participants had improved by at least one grade in mRS and by at least four points in NIHSS, relative to baseline. Together, these data suggest a single intravenous dose of allogeneic non-HLA-matched human UCB cells is safe in adults with ischemic stroke, and support the conduct of a randomized, placebo-controlled Phase 2 study.[25]

Just recently, scientists at Duke University in North Carolina began investigating the effect of cord blood on sufferers of adult ischemic stroke. In the study, 100 patients between 18 years and 90 years of age will undergo UCB transfusions between three and 10 days after their stroke. They will then be monitored for results.[26]

• In a study conducted at Stanford University School of Medicine, researchers injected into mice either cord blood plasma or blood from people aged between 19 years and 24 years or 61 years and 82 years. When the older mice received human UCB plasma every fourth day for two weeks, their memory, learning and hippocampal function improved notably, as well as their ability to navigate through a complex maze. Plasma from older people, on the other hand, was no help at all, while young adult plasma only induced an intermediate effect. After realizing something in the UCB was making the old brains act younger, the scientists discovered a protein called TIMP2, an important protein that vanishes as humans get older. Injecting TIMP2 by itself into elderly mice largely duplicated the beneficial effects of UCB. The Stanford team had already proved that young blood can reverse some of the signs of aging in mice but have never shown it could restore learning and memory.[27]

• A study conducted in 2015 examined whether transplanting UCB stem cells had positive, therapeutic effects on rat models with Parkinson's disease. They found the cord blood stem cells "significantly improve the motor deficits of the Parkinson's disease rats." According to the researchers, results suggest using cord blood stem cells "would have a significant impact on future strategies for Parkinson's diseases treatment."[28]

• A study conducted at the University of Illinois, Chicago, found stem cells from cord blood "re-educated" the immune system T cells of people with type 1 diabetes so their pancreas started producing insulin again, thereby reducing the amount of insulin they needed to inject. The small, open-label, Phase 1/Phase 2 study recruited 15 patients with type 1 diabetes aged 15 years to 41 years with a diabetic history ranging from one to 21 years. All but three of the patients (controls) underwent stem cell educator therapy once. Controls underwent a sham treatment in which they received no educated cells. The researchers checked the patients' progress at four, 12, 24 and 40 weeks after therapy. Six of the patients who had the therapy had some residual beta cell function (moderate type 1 diabetes) and the other six had no residual beta cell function (severe type 1 diabetes). Results showed the median daily dose of required insulin was down by 38 percent at week 12 for the six patients with moderate diabetes and by 25 percent for the patients with severe diabetes. There was no change in required insulin dose for the controls. Levels of C-peptide continued to improve at 24 weeks and were maintained to the end of the study at 40 weeks.[29]

While cord blood banks are essential to increasing patient access to transplant, the method in which cord blood is stored can be controversial.

• An infusion of cells from a child's own UCB appears to improve brain connectivity and motor function in children with spastic cerebral palsy, according to a randomized clinical trial. The placebo-controlled, Phase 2 trial included 63 children with varied types and severities of spastic cerebral palsy, a condition usually caused by brain damage before or at birth. Children who received one intravenous dose of at least 25 million stem cells per kilogram of their body weight saw improvements in motor function a year later. The improvements were greater than those typically observed for children of similar age and condition, and exceeded the gains made by children who received a lower dose of cells or a placebo.[30]

• In a study of the safety and efficacy of a novel therapeutic trial with UCB and concomitant recombinant human erythropoietin conducted in three cases of severe traumatic brain injury in rehabilitation, researchers found participants showed improvements during follow-up periods in various aspects. Patient 1 demonstrated improvements in motor and cognitive function, and diffusion tensor images showed increased nerve fibers. Patient 2 displayed improvements in activities of daily living. And in Patient 3, neurogenic fever vanished and brain PET revealed increased glucose metabolism at basal ganglia, thalami and cerebellum. There were no serious adverse events in any of the patients.[31]

The use of cord blood stem cells may extend beyond regeneration of healthy blood and immune systems.

• A Phase 1 clinical trial is seeking to enroll 10 children between 6 weeks to 6 years of age with less than 18 months of hearing loss with spoken language the intended end point. The trial, inspired by a Duke University study of 30 patients suffering from acquired hearing loss, shows cord blood transplants can be a treatment for sensorineural hearing loss due to mucopolysaccharidosis. The findings demonstrate hearing loss can be easily measured with a unit called ABR that is a count of functioning hair cells. If the transplant shows an improvement in ABR, it suggests the functioning hair cells are growing in number. In a previous trial, human UCB stem cells were used to treat hearing loss in a mice model, which resulted in replacement of hair cells. According to James Baumgartner, MD, a pediatric neurosurgeon at Florida Children's Hospital, "There was a pretty significant improvement, in particular if the stem cell transplant was done before 25 months of age."[32]

Expanding Uses for Diseases

It's been only approximately three decades since UCB was found to have lifesaving properties that can treat blood and immune system disorders. Since then, cord blood transplants have successfully treated thousands of patients afflicted with more than 80 diseases each year. Although cord blood transplants have many advantages over bone marrow transplants, including easy and painless collection, immediate use, partial match between donors and patients, lower rejection and disease transmission rates, and a larger pool of donors for ethnic minorities, they also have limitations that must be considered, including low volumes of HSCs, current inability to detect genetic diseases in the UCB and the unavailability of a second donation. Nevertheless, while cord blood banks and donations continue to expand, they will surely be needed since research continues to show promise for the use of cord blood stem cells to treat an ever-growing list of diseases. ❖

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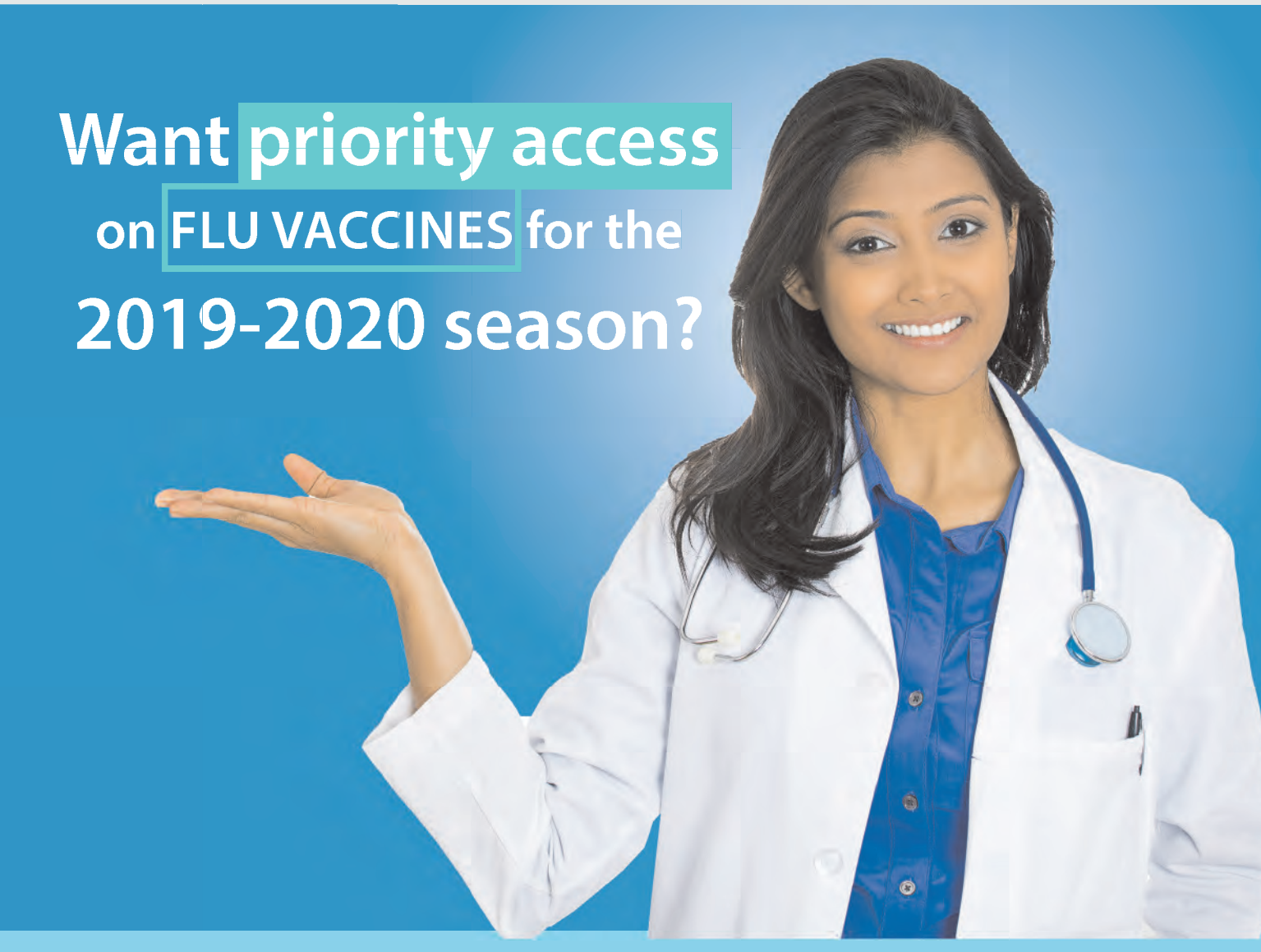

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Biosimilars:
From Concept to Reality

Approvals in 2018 brought the total number of U.S. Food and Drug Administration-licensed biosimilars well into the double digits — and more are in the pipeline.

By Trudie Mitschang

A BIOSIMILAR IS defined as a medicine similar to another, already-authorized biologic medicine (including vaccines, blood components, allergenics, somatic cells, gene therapies, tissues and recombinant therapeutic proteins). Biologics are different from conventional medications that are generally made from chemicals or are chemically synthesized. And, because biologics come from living organisms, they are variable in nature and their structures are generally more complex and not as easy to define and characterize. This complexity explains why developing biologics is a far more difficult process than manufacturing conventional drugs.

The United States market for biosimilars, sometimes dubbed "copycat" biologics, has been expanding at a rapid pace in recent years. In 2017 alone, the European Medicines Agency (EMA) approved 16 biosimilars for seven different originator products, and at least five of those — AbbVie's Humira (adalimumab), Genentech's Herceptin (trastuzumab), Biogen/Genentech's Rituxan (rituximab) and Eli Lilly's Humalog (insulin lispro) and Forteo (teriparatide) — previously had no biosimilars approval in Europe.[1] In a market long led by European innovation, the accomplishment was a significant one.

One of the catalysts for growth was attributed to the U.S. Food and Drug Administration's (FDA) withdrawal of its draft guidance on statistical methods used to evaluate the analytical similarity between branded drugs and biosimilars. The guidance, titled "Statistical Approaches to Evaluate Analytical Similarity," was initially issued in September 2017 and was intended to provide advice for biosimilar developers.[2] FDA withdrew its guidance following public input that expressed some concerns. One of the filers was Sarfaraz K. Niazi, an adjunct professor specializing in biosimilar development at the University of Illinois and the founder of Pharmaceutical Scientist Inc., a consulting company. In his petition, Niazi recommended FDA waive bridging studies for qualified non-U.S. comparators and encourage payers to reimburse only for biosimilars when prescribed for new patients.[2]

Regarding the decision, FDA Commissioner Scott Gottlieb noted, "One of the central aspects of biosimilar development and approval is the analytical studies performed to demonstrate that a biosimilar is highly similar to the reference product. We're taking a fresh look at our draft recommendations for evaluating analytical studies in order to ensure our guidance takes into consideration the most current and relevant science. … I believe that the FDA can do more to support the development of biosimilars, as well as promote the market acceptance of these products. As the cost to develop a single biosimilar product can reach hundreds of millions of dollars, it's important that we advance policies that help make the development of biosimilar products more efficient, and patient and provider acceptance more certain."[3]

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Lessons from the European Landscape

While notable advances in biosimilars are a recent development in the U.S., the products have been widely available in Europe for more than a decade. In 2003, the European Union created a legal pathway to the creation, approval and marketability of biosimilars. EMA, the European equivalent of FDA, was charged with the approval of biosimilars for use in European nations, while approval within specific countries could only be determined at the national level in each country. Following that decision, Omnitrope was the first biosimilar to be approved by EMA, and 19 additional biosimilars earned subsequent EMA approval.[4] Today, the European biosimilars market is the most mature in the world and continues to gather momentum. Overall, there are now more than 40 European Commission-approved biosimilar products across 15 different biologic classes (as of March 31, 2018).[4]

The advancement of biosimilars in the EU does not suggest the approval process is anything less than rigorous. Gaining approval for biosimilars under EMA guidelines requires a demonstration of how two products maintain a similar nature, and comparability studies are required for each biosimilar. To conduct this demonstration, at least eight key points must be addressed by both manufacturers and researchers:

Notable Names in the Biosimilar Development

A short "who's-who" list of trailblazers in this emerging market:

1. Novartis: The Swiss pharma has been at the forefront of biosimilar development in the U.S., securing approvals from the U.S. Food and Drug Administration (FDA) for biosimilars of Amgen's Neupogen (filgrastim) and Enbrel (etanercept). Novartis' Neupogen biosimilar, dubbed Zarxio, made history as the first biosimilar cleared by FDA and is one of only two biosimilars currently sold in the U.S. And, with approval of Erelzi, an Enbrel copy, Novartis owns two of the four biosimilars currently OK'd for use. Novartis isn't stopping there, either. The company said last summer it plans to launch five new biosimilar drugs by 2020.

2. Celltrion Inc.: Headquartered in Korea, Celltrion has a deep pipeline of biosimilar candidates. Its copy of Remicade was approved in Europe in 2013 and became just the second biosimilar to be approved in the U.S. last April. Under a partnership deal, Pfizer is in charge of marketing the biosimilar, named Inflectra, in the U.S. The pharma giant started shipping the drug to wholesalers in late 2017, and it currently sells it at a 15 percent discount to Remicade's wholesale acquisition cost.

3. Amgen: Amgen is on both sides of biosimilar development. On one hand, it has won FDA approval for the first biosimilar version of AbbVie's Humira (adalimumab), and it recently submitted an application for its copy of Roche's Avastin (bevacizumab), co-developed with Allergan. Yet, at the same time, it is working hard to defend its biologics-heavy portfolio from encroaching biosimilars developed by other drugmakers. Global sales of Enbrel, Neulasta and Neupogen combined to account for more than half of Amgen's revenues in the third quarter last year. All three are under biosimilar threat from either already approved biosimilars or biosimilar candidates in the pipeline.

4. Samsung Bioepis: Another Korean company, Samsung Bioepis is jointly owned by Samsung Biologics and Biogen. In short order, Bioepis has advanced its first cohort of biosimilar candidates to regulators and markets. Its Enbrel biosimilar has won approval in the European Union (as Benepali), Canada and Korea (as Brenzys), while its Remicade copy is OK'd for use in the European Union and Korea. Other candidates, including biosimilars of Herceptin and Humira, have been accepted for review by the European Medicines Agency.

1) The standard generic approach to defining a chemically derived medicine is not applicable to the production's means and capacity of biosimilars.

2) Demonstration must evaluate whether any significant changes are made within the manufacturing process.

3) Biosimilars must be similar in molecular structure and biological functionality.

4) The potency of the biosimilar and route of administration must remain the same as the originating biologic.

5) Deviations from the referenced product require justification and examination of how such deviations affect treatment with the biosimilar.

6) Biosimilars must be highly purified to remove any possible contaminated data from collection.

7) If any intended changes exist for the purpose of providing an added benefit and advantage to the patient, they are allowed. However, they must adhere to all other guidelines for biosimilars.

8) If a biosimilar is shown to be effective and safe in one setting, the data may be applied to other settings.

It is important to note that although biosimilars must undergo a two-stage approval process at the central level by EMA and the national level for each country, many healthcare entities have continued to express concern over issues like efficacy and patient safety. Healthcare providers, pharmacies and insurance companies all want to ensure postmarketing of a biosimilar does not place marketability above patient satisfaction and safety. These types of concerns are mirrored by stakeholders in the U.S.[4]

When it comes to cost, by nature, biosimilar production may be more expensive than traditional drugs. Yet, biosimilar producers in Europe routinely apply discounts to biosimilar production by as much as 45 percent, with some discounts going as high as 69 percent. According to Roche Chief Executive Severin Schwan, who faced biosimilar competition for two of the company's top cancer drugs from late 2017, competition is impacting discounts. "Analyst expectations now vary widely, with some saying 30 percent and others 60 percent," he said in an interview. "Personally, I think we will see material price effects because I believe in the power of markets and competition."[5]

With that in mind, the global market for biosimilars is expected to bring in sales in excess of $25 billion within the next five years.[4]

Obstacles and Opportunities

A number of significant challenges exist for manufacturers of biosimilars in the U.S. For example, FDA has not outlined what is required for a biosimilar to demonstrate interchangeability. Current guidance states an interchangeable product can be expected to produce the same clinical result as the reference. Unfortunately, to date, FDA has not granted a designation of interchangeability to any of the approved biosimilars.

Another challenge is extrapolating indications. For example, the biologic Remicade is approved in Europe for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, psoriasis and ulcerative colitis. The hope is that any biosimilar to Remicade, once it proves biosimilarity in one indication, would gain approval for all approved indications. According to FDA, this is potentially possible provided there is comparable evidence and adequate clinical and scientific justification. But, without the ability to extrapolate indications for existing biosimilars, development costs will be higher and the target market will be smaller. Analysts argue, however, that secondary indications typically add only 15 percent to 25 percent to sales revenue, making additional extrapolation testing less advantageous. In contrast, manufacturers maintain that not having all the indications could be perceived as a weakness in the final product.[6]

Using acceptable statistical models for equivalence studies and tailoring Phase III clinical studies has also been part of ongoing discussions surrounding biosimilars and their development. Getting investigators to agree on the appropriate evaluation models would allow an increased focus on addressing any remaining uncertainties surrounding efficacy, potentially reducing the size of large Phase III trials and, ultimately, saving time and costs.[6]

The Payer's Perspective

Without question, payers play a significant role in encouraging the adoption of biosimilars. According to a survey published by Amgen, payers in the U.S. do not expect the biosimilars market to mimic the generics market, and they also do not expect the U.S. biosimilars market to be comparable to the one in Europe.[7]

The survey of 40 different payers found payer perceptions of biosimilars include the following:

- Payers anticipate biosimilars will be a strategy to reduce specialty drug prices and most (88 percent) believe the category represents a compelling business opportunity.
- Eighty percent do not expect biosimilars to emulate the generics market. Instead, payers expect to consider them as lower-cost branded options.
- While there are analogues from the European commercial experience, at this time, few U.S. payers are relying on Europe's experience for U.S. forecasting.

The survey also showed that although U.S. payers are eager for biosimilars to reduce specialty drug prices, Europe's experience shows the level of savings may vary. European experience suggests the most important conditions for market uptake of biosimilars are driven by factors such as physician perception, patient acceptance, local pricing and reimbursement regulations, and procurement policies and terms. Amgen's research also indicates the U.S. path may share few characteristics with the global experience to date.[7]

A Learning Curve in the U.S.

Without question, the U.S. is still on a learning curve in the development of biosimilars. Regulators want more evidence regarding the quality of biosimilar products and their clinical impact on patients. On the other hand, investigators hope in the near future prescribers will develop increasing levels of comfort and experience using these newer therapeutic options in the U.S.

Without question, payers play a significant role in encouraging the adoption of biosimilars.

"All decision makers have a role in ensuring patients and healthcare systems see the full benefit of biosimilars. Policy frameworks need to be created in order to incentivize the use of biosimilars in both the near- and long-term," said Sheila Frame, vice president and head of Sandoz Biopharmaceuticals, North America. "We also need to continue to evolve our legal framework to prevent unnecessary delays related to intellectual property disputes and our regulatory, development and manufacturing processes as market dynamics change. Unbiased information should continue to be shared by credible sources, including EMA, FDA, health ministries, physicians, nurses and other key stakeholders.[8] ❖

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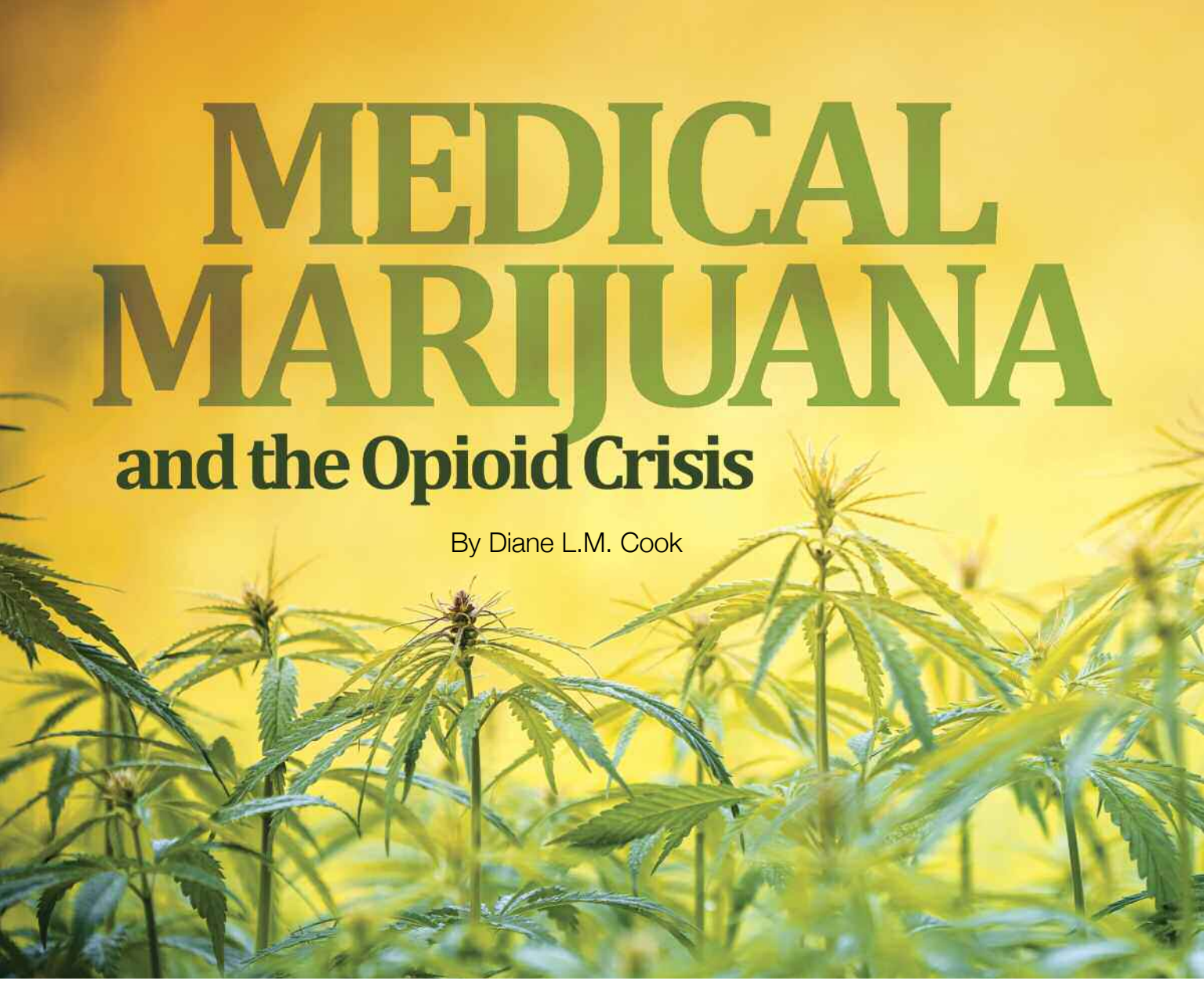
MEDICAL MARIJUANA and the Opioid Crisis

By Diane L.M. Cook



Can marijuana be used as an adjunct to or substitute for opioids in the treatment of chronic pain to potentially alleviate the opioid crisis?

BETWEEN 1999 AND 2014, the Centers for Disease Control and Prevention (CDC) reported sales of prescription opioids in the United States nearly quadrupled.[1] During this period, 351,630 deaths were attributed to opioid overdoses. In 2016, there was an average of 115 such deaths per day.[2] And, to date, this figure continues to escalate at an alarming rate.

The Opioid Crisis

According to CDC, prescription opioids are not the cause of the opioid crisis in this country. Instead, it cites illicitly manufactured fentanyl (IMF) — a synthetic opioid — as the main driver behind the crisis. Indeed, from 2012 to 2015, there was a 264 percent increase in synthetic opioid deaths. And, even though prescription opioid rates have fallen, overdoses associated with IMF have risen dramatically, contributing to a sharp spike in synthetic opioid deaths, as IMF is often mixed with heroin, counterfeit pills and cocaine with or without user knowledge.[3]

The reason opioid prescriptions nearly quadrupled between 1999 and 2014 is twofold. First, it was a response to patients who reported chronic pain to their doctors but were underprescribed pain medication. Second, millions of Americans experience severe or chronic pain due to myriad health conditions.[4]

According to the *Journal of Pain*, based on the 2012 National Health Interview Survey, 25.3 million American adults suffered from daily pain; 23.4 million American adults reported a lot of pain; 25.4 million American adults experienced category 3 pain;

and 14.4 million American adults experienced the highest level of pain, category 4.[5]

The five most common chronic pain conditions include chronic low back pain, chronic neck pain, fibromyalgia, osteoarthritis and tension headaches. Other highly painful conditions include multiple sclerosis and rheumatoid arthritis.

Marijuana As a Replacement for Opioids

To address the dramatically increasing number of opioid overdoses, researchers, doctors and chronic pain patients have asked if marijuana could be used as an adjunct to or substitute for opioids in the treatment of chronic pain, potentially alleviating the opioid crisis.

In fact, there is growing public and government support to use marijuana to treat chronic pain. A recent Gallup poll showed 64 percent of Americans are in favor of legalizing marijuana[6] and, as of June, 31 states plus Guam, Puerto Rico and the District of Columbia have legalized the medical use of cannabis. Fifteen other states have more restrictive laws limiting tetrahydrocannabinol (THC) content, for the purpose of allowing access to products that are rich in cannabidiol (CBD), a nonpsychoactive component of cannabis. As of January, nine states plus the District of Columbia have legalized the recreational use of cannabis, and another 13 states plus the U.S. Virgin Islands are considered to have decriminalized cannabis.[7]

In addition to public support, a growing body of research shows there is sufficient data to indicate marijuana could be beneficial in treating chronic pain, and by extension, potentially alleviate the current opioid crisis. Following are some findings:

• In a population-based, cross-sectional study in May, using the all-capture Medicaid prescription data from 2011 to 2016, medical marijuana laws and adult-use marijuana laws were associated with lower opioid prescribing rates (5.88 percent and 6.38 percent, respectively). The study's researchers said medical and adult-use marijuana laws have the potential to lower opioid prescribing for Medicaid enrollees, a high-risk population for chronic pain, opioid use disorder and opioid overdose, and marijuana liberalization may serve as a component of a comprehensive package to tackle the opioid epidemic. The researchers also said marijuana is one of the potential non-opioid alternatives that can relieve pain at a relatively lower risk of addiction with virtually no risk of overdose.[8]

• A study titled Health Effects of Cannabis and Cannabinoids: Current State of Evidence and Recommendations for Research conducted by the National Academies of Sciences, Engineering and Medicine in 2017 found there is conclusive or substantial evidence cannabis or cannabinoids are effective for treating chronic pain in adults. In addition, it said there is moderate evidence cannabis or cannabinoids are effective for improving chronic pain.[9]

• A study conducted in 2017 by Bradford and Bradford using quarterly data on all fee-for-service Medicaid prescriptions during 2007 through 2014 tested the association between medical marijuana laws and the average number of prescriptions filled by Medicaid beneficiaries. It found the use of prescription drugs was lower in states with medical marijuana laws than in states without them in five of the nine broad clinical areas studied.[10]

• In a study conducted by the University of Michigan in 2016, patients using medical marijuana to control chronic pain reported a 64 percent reduction in their use of more traditional prescription pain medications such as opioids. The 185 patients from a medical marijuana dispensary in Ann Arbor also reported fewer side effects from their medications and a 45 percent improvement in quality of life since using cannabis to manage pain. Researchers said their results suggest, for some people, medical marijuana may be an alternative to more common prescription painkillers.[11]

• In an April study, results from observational and retrospective studies showed people who use cannabis are more likely than people who do not to also use other drugs. People who take medical cannabis are also more likely to report medical and nonmedical

use of opioid analgesics, stimulants and tranquilizers. The researchers surmised given that people who take medical cannabis and those who do not are likely to have different underlying morbidity, it is possible medical cannabis use reduces prescription drug use, yet prescription drug use remains relatively high. They concluded studies comparing people who take medical cannabis with people who do not cannot draw conclusions about the effect of medical cannabis on drug use.[12]

In an April study, results from observational and retrospective studies showed people who use cannabis are more likely than people who do not to also use other drugs.

• In a study dated March 7, researchers stated the potential benefits of cannabis-based medicine (herbal cannabis, plant-derived or synthetic THC, THC/CBD oromucosal spray) in chronic neuropathic pain might outweigh their potential harms. According to the researchers, the quality of evidence for pain relief outcomes reflects the exclusion of participants with a history of substance abuse and other significant comorbidities.[13]

• A study conducted in 2012 by the Centre for Addictions Research of British Columbia in Canada stated there is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates to treat chronic pain. When used in conjunction with opiates, cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side effects) by patients in a clinical setting. Additionally, it found cannabinoids can prevent the development of tolerance to and withdrawal from opiates and can even rekindle opiate analgesia after a prior dosage has become ineffective. According to the researchers, novel research suggests cannabis may be useful in treating problematic substance use.[14]

The researchers say these findings suggest increasing safe access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the growing problematic use of pharmaceutical opiates. Despite a lack of regulatory oversight by federal governments in North America, they said, community-based medical cannabis dispensaries have proved successful at supplying patients with a safe source of cannabis within an environment conducive to healing, and may be reducing the problematic use of pharmaceutical opiates and other potentially harmful substances in their communities.[14]

• A systematic review and meta-analysis of cannabinoids for medical use conducted in 2015, which examined a total of 79 trials (6,462 participants) for several indications, including chronic pain, indicated there was moderate-quality evidence to support the use of cannabinoids for treating chronic pain.[15]

• In September 2017, the UCLA Cannabis Research Initiative (UCLA-CRI) was created at the UCLA Semel Institute for Neuroscience and Human Behavior. Its initial priorities are the therapeutic potential and health risks of cannabis and to provide education and research to lead public policy and public health decisions regarding cannabis.

The UCLA-CRI's first planned study is the world's first placebo randomized controlled clinical trial to evaluate whether cannabis can reduce or eliminate opioid use in chronic pain patients who have been using opioids long-term. Its second study is a prospective observational study of individuals who are opioid-dependent and are initiating cannabis use in an attempt to reduce or eliminate opioid use.

According to Jeff Chen, MD, director at UCLA-CRI, "There is substantial evidence that cannabis is effective for chronic pain, and there is emerging preliminary evidence that cannabis may be opioid-sparing. That is, when used in combination with opioids, cannabis may be able to reduce the amounts of opioids needed to achieve the same level of pain relief. There is also preliminary evidence that CBD possesses anti-addictive properties. And, there is preliminary evidence that cannabinoids may be able to reduce neuroinflammation, which is associated with chronic pain and chronic opioid use. Neuroinflammation is also associated with a host of psychiatric disorders such as depression and anxiety."

Igor Spigelman, PhD, a neuro-pharmacologist at UCLA-CRI, is conducting translational neurobiology research into disorders such as chronic pain, and he is currently leading the study titled Peripherally Restricted Novel Cannabinoids for the Treatment of Chronic Pain. "Specifically, Dr. Spigelman is working with a novel cannabinoid that has been modified so it does not cross the blood-brain barrier," said Dr. Chen. "Therefore, it cannot activate the cannabinoid type 1 receptors in the central nervous system, which means no psychoactivity. However, it can activate cannabinoid receptors in the periphery and, thus, reduce pain and inflammation."

The Future of Marijuana

Although there has never been a documented case of a marijuana overdose, some study results have provided negative and contradictory evidence such as how marijuana can help patients with chronic pain but it can cause adverse health effects,[18] or how marijuana can cure addiction to opioids but it can be addictive

itself. Most researchers agree much more research and clinical trials are needed before they can say for certain if marijuana can help treat patients with chronic pain or whether marijuana can help alleviate the current opioid crisis.

Stanford professor and drug policy expert Keith Humphreys described the studies concerning cannabis legalization and the decrease in opioid-related deaths and hospital admissions as falling victim to a form of logical error known as ecological fallacy: "It's correlation, not causation, because you cannot use statistical information about entire populations to understand individual behavior."[16]

And, Susan RB Weiss, PhD, director of the division of extramural research at the National Institute on Drug Abuse, who testified on "Researching the Potential Medical Benefits and Risks of Marijuana" before the Subcommittee on Crime and Terrorism on July 13, 2016, said "Promising preclinical findings do not always prove to be clinically relevant, and even fewer lead to new treatments."[17]

According to CDC, "Even though pain management is one of the most common reasons people use medical marijuana in the U.S., there is limited evidence that marijuana works to treat most types of chronic pain. A few studies have found that marijuana can be helpful in treating neuropathic pain. However, more research is needed to know if marijuana is any better or any worse than other options for managing chronic pain."[18]

The Cannabis and Cannabinoid Research (CCR) journal agrees: "More research is needed to better understand the efficacy, dose-response effects, routes of administration and side-effect profiles for cannabis products that are commonly used in the United States."

Yet, CCR adds, "Results from studies evaluating cannabis pharmacotherapy for pain demonstrate the complex effects of cannabis-related analgesia. There are multiple randomized controlled clinical trials that show cannabis as an effective pharmacotherapy for pain. However, further examination of preclinical studies of cannabis in pain models underscores the nuances of cannabis's analgesic and antihyperalgesic effects in animal models, and experimental research examining the effects of cannabis on human pain responding has focused either on healthy adults or clinical pain samples."

Most importantly, CCR says, "Further studies are necessary to further elucidate the role of cannabis as a potentially safer alternative to opioids for pharmacological pain management." And, it warns, "As cannabis use increases, additional research to support or refute the current evidence base is essential to attempt to answer the questions that so many healthcare professionals and patients are asking."[19]

Unfortunately, conducting more research can be problematic. Since 1970, marijuana has been designated a Schedule I drug under the Controlled Substances Act, which defines drugs under this designation as having high potential for abuse and no currently accepted medical use.[20] This designation results in barriers for researchers to conduct research and clinical trials on the plant because it is infinitely more difficult for them to obtain a research license and funding for a drug that is illegal. Currently, the University of Mississippi is the only federally approved marijuana grower, through its contract with the National Institute on Drug Abuse's Drug Supply Program, to supply researchers with highly controlled grown marijuana.[21]

Until the required research and clinical trials have been conducted, and the results have been carefully reviewed to show definitively that marijuana can be used as a treatment for chronic pain, and by extension alleviate the opioid crisis, the probability marijuana will remain designated a Schedule I drug is high. ❖

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Update on

Migraines have been around for thousands of years, and researchers have been studying them for decades, but their elusive causes remain unknown. Fortunately, many evolving treatments are reducing the frequency and pain of migraines, and an abundance of research persists.

By Jim Trageser

ONE OF MEDICINE'S enduring mysteries remains the underlying causes and a cure for debilitating migraines. Consequently, every physician has multiple patients suffering from migraine pain. The Migraine Research Foundation (MRF) reports 18 percent of adult American women suffer from migraines, as does 12 percent of the overall population. Migraines affect all ages and all ethnicities.

MRF contends that due to the severe pain and lost work time that results (90 percent of migraine sufferers can't work normally during an episode), migraines are among the top-10 most-disabling diseases on the planet.[1] It also reports there are 1.2 million hospital visits per year in the United States for severe migraines.

Indeed, JMS Pearce, the British neurologist who coined the term "migraine," pointed out some 30 percent of physicians may suffer from migraines. He wrote that the failure of medical science to determine the causes of or find a cure for migraines represents a "frustrated fascination" of those doctors who themselves suffer from them.[2]

Migraines

What Are Migraines?

Migraines are differentiated from other headaches by these features:

- A pronounced throbbing from the pain;
- A heightened sensitivity to lights and sounds;
- The length of the attack (generally lasting from four to 72 hours);
- A pattern of recurrence;
- Pain localized on one side of the head;
- Nausea (with vomiting easing the pain somewhat)[3]; and
- A preceding aura marked by visions of bright lights or jagged lines.[4]

Not all patients exhibit all of these symptoms, and symptoms may vary from one migraine episode to the next in the same patient.

Women are three times more likely to develop migraines than men, and an estimated 28 million women in the United States suffer from migraines. Up to 10 percent of children have migraines, with boys slightly more likely than girls to have them until the onset of puberty. A child with one parent with migraines has a 50 percent chance of developing them at some point. And, the likelihood is 75 percent if both parents have migraines.[1]

Migraines have been described since antiquity. Babylonian writings going back more than three millennia clearly describe the distinct symptoms of what we today refer to as migraines.[5] By 1200 B.C., Egyptian doctors were suggesting applying pressure to the skull to help relieve the pain.[6] About 400 B.C., Hippocrates also fully described migraines, including the aura, nausea and pain being confined to one side.[2]

The second-century A.D. Greek physician Claudius Galenus (better known as Galen of Pergamon) gave migraines their modern name when he referred to these unique headaches in Latin as hemi-crania (half cranium) — which was later anglicized into migraine. By the 17th century, migraines were well-accepted as a distinct category of headache.[2]

While migraines are not fatal, the so-far unknown underlying causes of migraines are associated with a higher risk of stroke and heart attack.[7] It's not necessarily a causal relationship, but the correlation seems fairly well-established. More recent research involving real-time brain scans and blood testing has helped further our understanding of the pathology of a migraine, if not yet illuminating its underlying causes.

There are other health risks associated with migraines: Depression is twice as prevalent in those patients with infrequent migraines, and four times as high in those with chronic migraines (four or more per month).[8] Asthma and migraines are also highly correlated, although again, the exact cause and effect is not understood.[9] The same is true with epilepsy.[10]

Causes of Migraines

While migraines are one of the most fully described of all medical afflictions, they remain among the least understood.

Researchers today believe the pain experienced during a migraine is caused by constriction of blood vessels in the brain — likely by changes in hormone levels, specifically serotonin and estrogen.[11] Advanced CT scans of patients during attacks have also indicated there is unusual electrical activity in the brain during a migraine.

Scientists do know some patients are more susceptible to having a migraine after certain events that may trigger its onset:[3]

- Hormonal changes (some women report they are more likely to experience a migraine at certain points in their menstrual cycle)
- Dietary changes (eating certain foods, skipping a meal or fasting can be associated with the onset of a migraine; some food additives — aspartame, monosodium glutamate — are also suspected triggers)
- Intense physical exertion
- Alcohol or medications
- Stress
- Changes in the weather
- Changes in sleep patterns[11]

Although the specific causes of migraines are not yet understood, researchers believe there is likely a genetic susceptibility since the condition runs in families.[3]

Symptoms and Progression of Migraines

Medical literature describes a migraine as a progression, usually broken into three segments, following in chronological order: prodrome, attack and postdrome.

Many migraine patients notice indicators that a migraine is imminent. And, while these differ from patient to patient, they often include neck stiffness, food cravings, moodiness, constipation, increased thirst and increased yawning.[12] A minority of patients (perhaps 20 percent, according to some researchers) will experience an aura before the attack begins. Most patients who have auras describe them as visual: a bright light or distorted vision. Others have other sensory disturbances: a feeling of being touched, weakness and difficulty speaking clearly. These typically last from 20 minutes to an hour.

The migraine itself is generally (but not always) marked by severe pain on one or both sides of the head, marked by a throbbing sensation. It is often accompanied by sensitivity to light, sound or other senses (smell or touch). Nausea is common. Less

frequently, patients experience blurred vision, light-headedness and sometimes even fainting. The attack, left untreated, can last from four hours to 72 hours. The postdrome, after the attack, can last for another 24 hours. Many patients report confusion or difficulty concentrating, dizziness, weakness, mood swings and sensitivity to light and sound.[13]

While most patients will see a drop in frequency and severity of migraines as they grow into their 60s and older, those with more frequent, painful migraines may actually see theirs become more frequent and severe — particularly without treatment.[14] A minority of patients experience an increase in frequency of up to 15 or more migraines per month, at which point they are said to have chronic migraines.[1]

While migraines are one of the most fully described of all medical afflictions, they remain among the least understood.

Diagnosing Migraines

Since the term migraine is a descriptive condition (based on symptoms, not pathology), diagnosis is made most often by a discussion of the patient's health history and symptoms. The patient may be referred to a neurologist to rule out other more serious conditions. An MRI or CT scan may be considered to eliminate the possibility of tumors, strokes, infections, parasites or bleeding. And, a spinal tap can help rule out infections or bleeding as their cause.[15]

Treating Migraines

Because the underlying causes of migraines remain undiscovered, treatment consists of alleviating symptoms and, possibly, preventing or lessening the severity of future attacks.

For mild migraines, over-the-counter pain relievers such as aspirin, ibuprofen and acetaminophen may be enough. However, overuse of these medications over time can lead to significant side effects such as ulcers and headaches.

More severe attacks may be treated with drugs designed specifically for migraines. One class of drugs, ergots (ergotamine and dihydroergotamine), is most effective in treating patients whose migraines occur frequently and typically last longer than 48 hours. These may be taken orally, by injection or via nasal inhaler.[15] They work by narrowing blood vessels.[16] Oftentimes, ergots are combined with caffeine to speed up their absorption into the bloodstream. Popular brand names of ergots combined with caffeine include Migergot and Cafergot. All of these can increase the nausea often associated with a migraine.

Another class of drugs used to treat migraines includes triptans, which also narrow blood vessels and block pain pathways. Triptans cannot be used in patients with coronary disease or a history of strokes. Popular brands include Imitrex (sumatriptan), Maxalt (rizatriptan), Axert (almotriptan), Amerge (naratriptan), Zomig (zolmitriptan), Frova (frovatriptan) and Relpax (eletriptan). Treximet is a popular combination of sumatriptan and naproxen sodium.[15]

For patients not eligible for either triptans or ergots, more powerful narcotics are sometimes prescribed. However, because of the side effects of opiates and opioids and the danger of addiction, it is advised these classes of drugs not be used long-term.

A drug normally prescribed to treat high blood pressure, Zestril (lisinopril), has been shown to lessen the length and severity of migraines in some patients.[15]

Due to the numerous side effects of all of the drugs used to relieve the symptoms of migraines, physicians usually work with their patients to create a treatment regimen that includes long-term prevention of future attacks.

Preventing Migraines

While modern painkillers can help ease migraine symptoms, many patients can avoid future migraines or suffer less severe attacks by following a preventive regimen. Unfortunately, there is no vaccine to give permanent protection, but there are a variety of prescriptions, exercises and lifestyle changes that can combine to lower the risk of future migraines. Those with frequent migraines (four or more a month) are encouraged to consider a prevention approach.[15] Depending on the severity of the attacks and any other health issues, physicians may prescribe one of the following treatments:

Cefaly. An external neurostimulation device, the recently approved Cefaly is effective in some patients with episodic (nonchronic) migraines. Available only with a prescription, the device is worn with or without a band around the head with an electrode positioned over the forehead. Small electrical impulses are then sent through the skin, which seems to help many sufferers.[17] While the manufacturer claims Cefaly also helps reduce the pain of ongoing attacks, the researchers cited in this footnote felt it was more effective at prevention than pain relief.

Erenumab. Earlier this year, the U.S. Food and Drug Administration (FDA) approved the first drug specifically

designed and shown effective at preventing migraines. Sold under the brand name Aimovig, it works by blocking the calcitonin gene-related peptide (CGRP).[4] The drug is self-administered monthly via injection.

Then, in September, FDA approved a second drug, Ajovy (fremanezumab), for migraine prevention. The monoclonal antibody that also works by blocking the CGRP is the only one of its kind to offer quarterly and monthly dosing options.[18]

Antidepressants. Because some antidepressants work by regulating levels of serotonin, they can also help prevent migraines. Amitriptyline, a tricyclic drug, is currently approved by FDA for use in preventing migraines. Other tricyclic antidepressants are sometimes used as they can have fewer side effects (sleepiness, constipation and weight gain are associated with Amitriptyline).[15] However, the Mayo Clinic advises against using another class of antidepressants known as selective serotonin reuptake inhibitors since these can actually trigger a migraine or make the next one more painful.

Cardiovascular drugs. Two classes of drugs originally developed to treat high blood pressure have shown to be effective at preventing migraines in some patients. Three beta blockers are currently prescribed to prevent migraines: propranolol, metoprolol tartrate and timolol. When taking these, there is typically a several week period before improvement is noted. Patients who have an aura before a migraine may see improvement with verapamil (Calan and Verelan).[15]

Epilepsy drugs. Two antiseizure medications used in treating epilepsy have proved to reduce the frequency of future migraines in some patients. Valproate and topiramate have both been shown to be effective, but they also have significant side effects. Valproate should not be used by women who are or may become pregnant. It can cause nausea, tremor, weight gain, dizziness and loss of hair. Topiramate can lead to diarrhea, weight loss, nausea and memory issues.[15]

Botulinum toxin A. Sold under the brand name Botox, this derivative of the fatal bacterium Clostridium botulinum (the microbe that causes botulism) has been shown to be effective at reducing the frequency and pain of attacks in patients with chronic migraine.[19]

While the above medications and devices can help reduce the frequency and pain of future migraine attacks, most physicians will want to couple them with behavioral modification plans to further their effectiveness. These changes may include eating regularly scheduled meals, drinking plenty of liquids, getting regular rest and exercising consistently. Women whose attacks are tied to their menstrual cycle may be candidates for hormone therapy.[4] Also, physicians will want to review a patient's current maintenance prescriptions to see if any of those medications may worsen or even trigger migraine attacks.

Another part of prevention is learning to avoid, where possible, known triggers. To identify triggers specific to each patient, a migraine log may help. This entails a patient keeping a diary of daily events (meal times, sleep times, exercise, job stress, etc.) to try to isolate anything that may be triggering the migraines.[20]

Ongoing Research

The lack of specific knowledge of the underlying cause of migraines isn't for absence of research. Hundreds of studies are listed on ClinicalTrials.gov for migraine basic research, improved treatments and prevention.

One of the more interesting areas of study is the intersection between migraine and epilepsy. As noted above, several drugs used to treat epilepsy are also effective in treating migraines. And, it has been known for several years that epileptics are more likely than the general population to suffer from migraines, and migraine patients have a higher incidence of epilepsy. In fact, their symptoms can be so similar there is often misdiagnosis between the two conditions.[10] Researchers are looking into whether both diseases could be caused by a common set of factors.

Other researchers are investigating a genetic link. Many migraine patients seem to have a common mutation in the TRESK gene that governs a critical potassium ion channel. This mutation may make brain cells more sensitive to pain.[10]

Researchers at the University of Michigan are using MRI and PET scans to map the brains of patients with migraines in hopes that other researchers will be able to use the data to gain additional insights into the physiology of migraines.[21]

As of this writing, Ionis Pharmaceuticals is recruiting subjects for a clinical trial of its IONIS-PKKRx, an RNA-targeted antisense drug designed to fight migraines by slowing production of prekallikrein, a necessary component of serine protease.[22]

Biohaven Pharmaceuticals is testing Rimegepant that, like the already approved Aimovig, is in a class of calcitonin gene-related peptide blockers.[23]

A professor at the University of Valencia in Spain is analyzing data from a study on whether a specific regimen of physical therapy involving stretching and exercise of certain neck muscles could help prevent or lessen the severity of future migraine attacks.[24]

UCLA researchers are conducting a blind test to see if melatonin, a hormone associated with sleep cycles, may be effective at helping reduce migraines in adolescents.[25]

And, while mechanical implants (similar in concept to the Cefaly device, but implanted under the skin like a pacemaker) have been under study since 1977, they have yet to come to market. However, research into these occipital nerve stimulation implants continues.[26]

Looking Ahead

While researchers are ever closer to discovering the root causes of migraines and, hopefully, a permanent cure, they are not there yet. For now, physicians will continue to work with patients to alleviate pain and help prevent future attacks through a regimen of treatment and behavior modification. ❖

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Myths and Facts: Complex Regional Pain Syndrome

Better understanding of this debilitating and painful condition stemming from a previous trauma is needed to demystify it and dispel the mistaken notion that the suffering is all in one's head.

By Ronale Tucker Rhodes, MS

SAMANTHA REEB WAS an active college freshman and just beginning her adult life when it "changed in the blink of an eye." The van that she and seven of her high school friends were riding in was rear-ended by a driver traveling 60 mph. Regrettably, none of the teens was wearing a seatbelt, and all were badly injured. Samantha's legs were badly injured and, afterward, she was in excruciating and unrelenting pain that left her unable to walk. But, doctors couldn't tell her why, and her first doctor even claimed she was simply making it up. Until, finally, she was diagnosed with complex regional pain syndrome (CRPS). After numerous medications and spinal injections, none of which worked, she was referred to a pain clinic, where she learned to manage her pain and walk again. "Even though I was stuck with this horrible pain for the rest of my life, I put in so much hard work, and I finally got something back," explains Samantha. "At that point, I realized something: I could either live the rest of my life feeling sorry for myself, or I could live the rest of my life. So that is what I chose to do."[1]

Table 1. International Association for the Study of Chronic Pain CRPS Clinical Diagnostic Criteria

A clinical diagnosis of CRPS can be made when three of the four symptom categories and two of the sign categories are met:

- Continuing pain that is disproportionate to any inciting event
- At least one symptom reported in at least three of the following categories:
  - Sensory: Hyperesthesia or allodynia
  - Vasomotor: Temperature asymmetry, skin color changes, skin color asymmetry
  - Sudomotor/edema: Edema, sweating changes or sweating asymmetry
  - Motor/trophic: Decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia) or trophic changes (e.g., hair, nail, skin)
- At least one sign at time of evaluation in at least two of the following categories:
  - Sensory: Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
  - Vasomotor: Evidence of temperature asymmetry (>1°C), skin color changes or asymmetry
  - Sudomotor/edema: Evidence of edema, sweating changes or sweating asymmetry
  - Motor/trophic: Evidence of decreased range of motion, motor dysfunction (e.g., weakness, tremor, dystonia) or trophic changes (e.g., hair, nail, skin)
- No other diagnosis better explaining the signs and symptoms

In addition, a slightly modified version of the above listing is used for CRPS research (as opposed to clinical) criteria. For these rules, one must have the CRPS characteristics present in all four of the symptom categories and in at least two out of the four sign categories.

Source: Wheeler AH. Complex Regional Pain Syndromes. Medscape, Jan. 2, 2018. Accessed at emedicine.medscape.com/article/1145318-overview.

CRPS is a progressive disease of the sympathetic nervous system. Those affected by CRPS have pain characterized as constant, extremely intense and out of proportion to the original injury. It is ranked by the McGill Pain Index as the most painful form of chronic pain that exists today.[2] "Most people wouldn't last 10 minutes in the shoes of someone who feels the pain we do," says Samantha. "We live every day with more pain than a cancer patient or a woman in labor or someone getting an amputation."

There are two types of CRPS. CRPS type I, previously known as reflex sympathetic dystrophy (RSD), involves injuries to the soft tissue of the affected area. Soft tissue injuries can include sprains, burns, tears and strains, and they can occur due to inflammation of body parts such as arthritis, bursitis and tendonitis. CRPS type II, previously known as causalgia, involves damage to at least one major nerve that has been clearly defined, and its cause may or may not be known.[3]

While CRPS can occur in anyone, it is more common in women, and it can occur at any age, most commonly in individuals aged 40 years to 60 years. It is very rare in the elderly, and few children under age 10 years and almost no children under age 5 years are affected.[3,4] Data collected by the National Institute of Neurological Disorders and Stroke (NINDS) on the occurrence of CRPS in patients with nerve injury and paralysis found CRPS develops in roughly 2 percent to 5 percent of patients who experienced peripheral nerve injury and roughly 12 percent to 21 percent of patients with hemiplegia (a form of paralysis that affects one side of the patient's body).[3]

While the National Organization for Rare Disorders and the U.S. Food and Drug Administration (FDA) recently designated CRPS a rare disease, meaning there are fewer than 200,000 cases in the U.S., the exact number of persons affected by CRPS today is not known due to a lack of understanding about it in the medical community — despite criteria explicitly defined by the International Association for the Study of Pain (IASP) (Table 1).[5] As such, increased awareness is needed about the real facts behind this disease.

Separating Myth from Fact

Myth: CRPS is a new and rare disease.

Fact: CRPS was first written about by Silas Mitchell Weir, MD, and colleagues during the Civil War. Dr. Weir, a U.S. Army contract physician who treated soldiers with gunshot wounds, described in his book *Gunshot Wounds and Other Injuries of Nerves* pain that persisted long after bullets were removed from the bodies of soldiers. He noted the pain was characteristically of a burning nature, and named it causalgia (Greek for burning pain), which he

attributed to the consequences of nerve injury. Since that time, many other physicians have written about CRPS, calling it post-traumatic dystrophy, shoulder-hand syndrome and RSD.[6]

As stated previously, while FDA has declared CRPS a rare disease, some studies provide evidence that CRPS is not rare at all, especially CRPS type I. A Korean study showed 42 of 477 (8.8 percent) surgically treated wrist fracture patients developed CRPS type I, specifically among females with a high-energy wrist trauma or a severe communicated fracture. A Dutch study reported similar results with 42 of 596 (7 percent) fracture patients developing CRPS type I following emergency room treatment using the Harden and Bruehl diagnostic criteria. Yet, if the IASP criteria had been applied in the study, 289 of the same 596 fracture patients (48.5 percent) would have been deemed to have CRPS type I after treatment. And, in 2015, an Italian study reported CRPS occurred in anywhere from 1 percent to 37 percent of all fractures following orthopedic surgery, depending on the severity of the fracture.[7]

Myth: CRPS is a psychiatric disorder.

Fact: There is some debate about whether CRPS is a legitimate chronic pain condition versus a result of a patient's psychiatric state. But, studies show patients with CRPS undergo physical changes to the nervous system and bones, joints, muscles and nerves in the affected area, making CRPS a purely psychosomatic disorder highly unlikely.[8] Indeed, common features of CRPS are very visible, including:[4]

- Changes in skin texture on the affected area (it may appear shiny and thin);
- Abnormal sweating pattern in the affected area or surrounding areas;
- Changes in nail and hair growth patterns;
- Stiffness in affected joints;
- Problems coordinating muscle movement, with decreased ability to move the affected body part; and
- Abnormal movement in the affected limb, most often fixed abnormal posture (dystonia), but also tremors in or jerking of the limb.

Myth: CRPS is caused only by major injuries.

Fact: Actually, in more than 90 percent of cases, CRPS is caused by trauma or injury, the most common of which are fractures, sprains/strains, soft tissue injury (burns, cuts, bruises), limb immobilization (such as being in a cast), surgery or even minor medical procedures such as a needlestick.[4] Of course, CRPS can also be caused by a major trauma or even a heart attack or stroke.[9]

What is unclear is why some people develop CRPS while others who experience similar trauma do not. One theory suggests pain receptors in the affected body part become responsive to catecholamines (a family of nervous system messengers). In animal studies, norepinephrine (a catecholamine released from sympathetic nerves) acquires the capacity to activate pain pathways after tissue or nerve injury.[10] Another theory is CRPS is caused by an immune response. Individuals with CRPS have high levels of cytokines (inflammatory chemicals) that contribute to redness, swelling and warmth reported by many patients. In fact, CRPS is more common in individuals with other inflammatory and autoimmune conditions.[4]

Another cause of CRPS is genetics since rare family clusters have been reported. And, in some cases, CRPS develops without any known injury, but by an infection, blood vessel problem or entrapment of nerves causing an internal injury.[4]

Myth: CRPS types I and II have different symptoms.

Fact: The only difference between CRPS types I and II is the known cause. As stated earlier, if nerve injury is confirmed, it is known as CRPS type II, whereas if there is no confirmed nerve injury, it is known as CRPS type I.

Both types of CRPS have four main symptoms:[2]

- Constant chronic burning pain that is usually significantly greater than the original event or injury. While the affected area may feel cold to the touch, it feels to patients as though it is on fire. In addition, patients experience allodynia, which is an extreme sensitivity to touch, sound, temperature and vibration.
- Inflammation that can affect the appearance of the skin, bruising, mottling, tiny red spots, shiny, purplish look and skin temperature that can cause excessive sweating.
- Spasms in blood vessels (vasoconstriction) and muscles of the extremities.

The American Journal of Medicine reports that spread of CRPS has been recognized since 1976.

- Insomnia and emotional disturbance that can include major changes to the limbic system such as short-term memory problems, concentration difficulties, sleep disturbances, confusion, etc.[11] Other symptoms can include changes in nail and hair growth patterns, stiffness in affected joints and problems coordinating muscle movement, with decreased ability to move the affected body part.[4]

Myth: CRPS will not spread from its original location.

Fact: The *American Journal of Medicine* reports that spread of CRPS has been recognized since 1976.[12] In fact, wherever there is a nerve, it can spread. In 70 percent or more of CRPS cases, pain starts in one part of the body and then spreads depending on the type of the original injury, treatments used, medical history and subsequent injuries. In most cases, it follows very specific paths

such as from hand to arm or foot to leg. But, it can also spread from one side to another such as from the left foot to right foot or right hand to left hand. In addition, it can spread up the arm from the hand in what was once referred to as shoulder-hand syndrome.[13] In about 8 percent to 10 percent of cases, it can become systemic (body wide),[11] but this is more likely to happen when a spinal injury is involved.[12] In worst cases, it affects completely healthy internal organs as well.[14]

Myth: CRPS resolves itself quickly.

Fact: There is debate concerning this myth, too. The prognosis for people with CRPS varies from person to person. Spontaneous remission does occur in some, but in others it persists for years. A recent systematic review of CRPS found evidence to suggest this discrepancy may "be due to a substantial number of cases resolving with limited or no specific intervention early in the course of the condition, with a smaller subset of more persistent cases being seen in tertiary care pain clinics." For example, one study followed 30 patients with post-traumatic CRPS without treatment for an average of 13 months that found CRPS resolved in 26 of the 30 patients (the other four patients were withdrawn from the study to be given treatment). Another prospective study of 60 consecutive patients with tibial fracture who underwent standard care found 14 of the 18 patients diagnosed with CRPS at bone union were free of CRPS at one-year follow-up. However, researchers did note that neither of the studies used the IASP diagnostic criteria, which may have influenced the results.

In contrast, the same systematic review found much lower resolution rates in chronic CRPS patients even with specialty pain care. In one study of 102 patients over an average six-year follow-up, 30 percent reported resolution using the IASP criteria, 16 percent reported progressive deterioration, and the remaining 54 percent reported stable symptoms.[15] In the Dutch study mentioned earlier, all patients who developed CRPS type I after fracture and treatment still had ongoing severe pain and other symptoms that persisted even at one-year follow-up.[7]

Myth: CRPS pain cannot be treated with opioids.

Fact: This myth is also debated due to the potentially harmful effects of opioids, as well as results from only one small randomized controlled trial of 43 patients conducted to determine opioids' efficacy, which showed no significant analgesic effects of sustained release morphine (90 mg per day) over eight days.[15] However, opioids are an effective treatment for many pain conditions. Unfortunately, no long-term studies of oral opioid use in treating neuropathic pain, including CRPS, have been performed. Even so, most experts believe opioids should be given as part of a comprehensive pain treatment program for CRPS. And, they should be prescribed immediately if other medications do not provide sufficient analgesia.[16]

Today, there is a lack of information about the pathophysiology of CRPS, and there are no consistent objective diagnostic criteria, which makes clinical trials that demonstrate effective therapies difficult to perform. As such, it is generally agreed CRPS must be treated with a multidisciplinary approach with the goal to control pain, with best results if treatment begins early when symptoms begin. A combination of therapies is typically necessary, including medications, physical and occupational therapy, interventional procedures, and psychosocial/behavioral management.[17]

While no drug is approved by FDA to treat CRPS, several classifications of medications are reported to be effective. However, it should be noted that no single drug or combination of drugs works for every person. Medications to treat CRPS include bisphosphonates (e.g., high-dose alendronate or intravenous pamidronate); nonsteroidal anti-inflammatory drugs (e.g., over-the-counter aspirin, ibuprophen and naproxen); corticosteroids that treat inflammation/swelling and edema (e.g., prednisolone and methylprednisolone); drugs initially developed to treat seizures or depression now known to be effective for neuropathic

Organizations Supporting CRPS

American Chronic Pain Association
P.O. Box 850
Rocklin, CA 95677-0850
(800) 533-3231
(916) 632-0922
ACPA@theacpa.org
theacpa.org

American RSD Hope Group
P.O. Box 875
Harrison, ME 04040-0875
(207) 583-4589
www.rsdhope.org

Pain Relief Foundation
Clinical Sciences Centre
University Hospital Aintree, Lower Lane
Liverpool L9 7AL
United Kingdom
(0151) 529 5820
secretary@painrelieffoundation.org.uk
www.painrelieffoundation.org.uk

Reflex Sympathetic Dystrophy Syndrome Association of America
PO Box 502
Milford, CT 06460
(877) 662-7737
(203) 877-3790
info@rsds.org
www.rsds.org

pain (e.g., gabapentin, pregabalin, amitriptyline, nortriptyline and duloxetine); botulinum toxin injections; opioids (e.g., oxycodone, morphine, hydrocodone and fentanyl); N-methyl-D aspartate receptor antagonists (e.g., dextromethorphan and ketamine); and topical local anesthetic creams and patches (e.g., lidocaine).[4]

Physical therapy can help to keep the painful limb or body part moving and can improve blood flow and lessen circulatory symptoms. It can also improve the affected limb's flexibility, strength and function. Occupational therapy can help individuals learn new ways to work and perform daily tasks.[4]

Interventional pain management procedures are often used when conservative treatment options fail to provide adequate pain relief and restoration of function. These procedures include sympathetic nerve blocks, chemical and surgical sympathectomy, intravenous regional anesthesia, intravenous infusion, spinal cord stimulation, intrathecal medication and amputation.[18]

Psychotherapy is recommended because CRPS is often associated with profound psychological symptoms, including depression, anxiety and post-traumatic stress disorder, all of which heighten the perception of pain and make rehabilitation efforts more difficult.[4]

Lastly, there are a number of emerging treatments:[4]

• In a small trial in Great Britain, 13 patients with CRPS who did not respond well to other treatments were given low-dose intravenous immune globulin for six months to 30 months. Results showed a greater decrease in pain scores than those receiving saline during the following 14 days after infusion.

• In patients who have not responded well to other treatments, intravenous ketamine (a strong anesthetic) in low doses for several days to either substantially reduce or eliminate the chronic pain of CRPS is shown to be useful.

• Several studies have demonstrated reduced pain with the use of graded motor imagery therapy, which includes performing mental exercises such as identifying left and right painful body parts while looking into a mirror and visualizing moving those painful body parts without actually moving them.

• Alternative therapies also sometimes work, including behavior modification, acupuncture, relaxation techniques and chiropractic treatment.

Dispelling the Myths Now

The pain is all too real for patients suffering from CRPS, evidenced by visible signs and symptoms. Unfortunately, little is known about the condition, and little research has been conducted due a lack of understanding about the physiological processes associated with it.

Fortunately, there are studies and organizations working to overcome these obstacles to help patients. Currently, a number of clinical trials are being conducted, including a Phase II trial of an oral non-opioid investigational medication and another investigating a medical device to manage pain associated with CRPS. Another promising therapy (Neurotropin) used extensively in Japan to treat CRPS and other painful conditions is being clinically studied by NINDS.[19] IASP has instituted a special interest group on CRPS as a forum for members to engage in free and frank communication on the diagnosis and management of CRPS, bring focus to new developments, and assimilate the views of the different medical disciplines and patient reports about pain and the sympathetic nervous system.[20]

The designation of CRPS as an official rare disease in 2014 also holds promise. It could provide strong incentive for new drug development for this disease since FDA will accept clinical trials with fewer patients, making them more feasible, quicker and cheaper for manufacturers. In fact, the designation spurred a CRPS clinical trial to evaluate the efficacy and safety of neridronate, a new bisphosphonate that has been shown to significantly reduce pain compared to placebo, which led to the drug's approval in Italy, China, Hong Kong and Taiwan.[21] A second clinical trial of the drug is currently recruiting.[22]

It is hoped that between ongoing research and the rare disease designation, more will be learned about this painful condition, and improved treatments will become available. ❖

RONALE TUCKER RHODES, MS, is the editor of *BioSupply Trends Quarterly*.

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Subcutaneous Immune Globulin Maintenance Therapy for CIDP:

An Idea Whose Time Has Come

By Keith Berman, MPH, MBA

MOST OFTEN DIAGNOSED in people between 40 years and 60 years of age, chronic inflammatory demyelinating polyneuropathy (CIDP) is a relatively rare immune-mediated peripheral nervous system disorder that results in variable loss of grip strength and upper and lower limb weakness. Patients may find themselves unable to get up from a sitting position, maintain balance or handle small or delicate items. If left untreated, irreversible axonal damage can occur, with cumulative disability that eventually leads to wheelchair dependence in about one-third of patients.

While its exact mechanism of action remains unclear, intravenous immune globulin (IVIG) has consistently been shown in well-designed clinical trials to be effective in durably reducing disability in roughly one-half of affected patients.[1,2] As maintenance therapy to prevent disease relapse, IVIG is preferred

over corticosteroids, plasma exchange or immunosuppressive drug options.

But the benefits of long-term IVIG administration often come with significant downsides. Even after employing available strategies such as slowing the infusion rate or switching product brands, some patients suffer systemic reactions that can include headache, fatigue, fever, chills, hypotension, tachycardia, myalgia, lower-back pain, rash, flushing, nausea and vomiting. Particularly in patients with predisposing risk factors, IVIG administration has also been associated with serious systemic adverse events, including renal insufficiency and, in rare instances, thrombosis or anaphylactoid reactions. In the clinic or home setting, IVIG must be infused by a specially trained nurse, and the patient must adhere to a set scheduled infusion regimen.

As documented in several recent pivotal clinical trials, a potential solution for CIDP patients with these IVIG-related issues is the same one that works for many primary humoral immunodeficiency (PI) patients who require IgG replacement therapy: self-administered subcutaneous immune globulin (SCIG).

A recent investigation randomized 30 CIDP patient responders to IVIG for a switch to a corresponding total dose of SCIG administered thrice-weekly at home or to thrice-weekly subcutaneous saline. The SCIG group experienced a modest 5.5 percent mean improvement in isokinetic muscle strength, versus a 14.4 percent mean decline in the placebo group.[3] More recently, a meta-analysis of eight studies comparing the efficacy and safety of IVIG and SCIG in patients with CIDP or multifocal motor neuropathy (MMN), another chronic inflammatory demyelinating neuropathy, found no significant differences in muscle strength outcome; SCIG therapy was associated with a significantly reduced risk of moderate and/or systemic side effects.[4]

In March 2018, based on results from the double-blind, placebo-controlled Phase 3 PATH trial,[5] CSL Behring's 20% SCIG product (Hizentra), approved in 2010 for the treatment of PI, became the first to secure an additional indication for the treatment of adults with CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment. Another SCIG product already approved for PI, Shire's HyQvia, is currently being investigated for use as CIDP maintenance therapy. By all accounts, SCIG is already gaining popularity among patients and physicians as the IgG maintenance treatment of choice.

> "A potential solution for CIDP patients with these IVIG-related issues is the same one that works for many primary humoral immunodeficiency patients who require IgG replacement therapy: self-administered subcutaneous immune globulin."

"Maintenance SCIG therapy is a potential option for any CIDP patient who requires ongoing treatment, and is willing to learn how to self-administer the product at home," said Leslie Vaughan, chief operations officer at NuFACTOR Specialty Pharmacy. But, she added, most patients who decide to switch to SCIG therapy from nurse-managed home or clinic-based IVIG infusions appear to be motivated by one or more of these reasons:

- Poor tolerance to systemic side effects during or shortly after IVIG infusion
- Poor venous access necessitating placement of a vascular access device
- A desire for more flexibility in scheduling infusions to minimize work/lifestyle conflicts
- A desire to be independent of the need for nurse-managed clinic or home infusion visits

Divided SCIG Doses Reduce Systemic Reactions

Following a typical 2 gram per kilogram (g/kg) induction dose of IVIG, most responders receive maintenance therapy infusions of greater than or equal to 1 g/kg of body weight every three to four weeks,* under the management of a nurse infusion specialist in the home or in the clinic setting. IVIG administration results in immediate (within six hours) or delayed systemic adverse reactions in roughly 5 percent to 15 percent of infusions, affecting as many as 20 percent to 40 percent of all patients.[6] By contrast, across five case series evaluating SCIG in PI patients, the reported rates of systemic adverse reactions ranged between zero and less than 1 percent.[7] The largest of these studies, monitoring 33,168 SCIG

** Some CIDP patients may require IVIG infusions as often as every two weeks or as infrequently as every eight weeks.*

Intravenous and Subcutaneous Immunoglobulin Products Approved for CIDP or in Clinical Testing

Product	Delivery form(s)[1]	Indication	Approval/ Study Phase
GAMUNEX-C Immune Globulin Injection (Human), 10%	IV SC	Treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse [*IV administration form only*]	Approved September 2008
Privigen Immune Globulin Intravenous (Human), 10%	IV	Treatment of adults with CIDP to improve neuromuscular disability and impairment	Approved September 2017
Hizentra Immune Globulin Subcutaneous (Human), 20% Liquid	SC	Treatment of adult patients with CIDP as maintenance therapy to prevent relapse of neuromuscular disability and impairment	Approved March 2018
GAMMAGARD LIQUID Immune Globulin Infusion (Human), 10%[2]	IV SC	Treatment of CIDP [*IV administration form only*]	Phase 3 clinical testing
HyQvia Immune Globulin Infusion (Human) 10% with Recombinant Human Hyaluronidase	SC	Maintenance therapy to prevent relapse of CIDP	Phase 3 clinical testing

[1]IV = intravenous; SC = subcutaneous
[2]GAMMAGARD LIQUID (administered intravenously) is also indicated as a maintenance therapy to improve muscle strength and disability in adult patients with multifocal motor neuropathy (MMN).

infusions in 158 patients, documented a systemic adverse reaction rate of just 0.3 percent: 100 mild and six moderate events in 28 patients with no severe or anaphylactoid reactions.[8]

"Patients on SCIG therapy experience far fewer systemic side effects such as headache, nausea, chills and fatigue because the IgG is administered subcutaneously in frequent, much smaller doses than IVIG," explained Vaughan. While local swelling, itching, heat, pain and erythema reactions at the SCIG infusion site are common, they generally resolve within 12 hours to 24 hours without treatment and tend to diminish over time. These typically mild local reactions are rare with IVIG infusion.[9]

SCIG therapy delivers a similar quantity of IgG as IVIG over the same three- or four-week period, but the peak serum IgG level is much reduced by dividing the IVIG dose into one or more doses a week; a common twice-weekly SCIG infusion schedule, for example, divides a monthly IVIG dose into eight much smaller doses. The serum IgG peak following each of these small subcutaneous infusions is additionally moderated by its relatively slow absorption into the bloodstream. Because the large IgG protein is unable to cross capillary endothelial walls to directly enter the circulation, it instead slowly transits through the lymphatic system.[10] The serum IgG level peaks between 48 hours and 72 hours following an SCIG infusion.

A combination of small divided doses and slow absorption appears also to diminish the severity of the infrequent systemic events that occur with SCIG. Danish investigators recently examined two of the most common side effects of IVIG — headache and nausea — in 59 patients diagnosed with CIDP, MMN or postpolio syndrome treated with IVIG, and 27 CIDP and MMN patients treated with SCIG. Patients reported symptom severity on a visual analogue scale (VAS) from 0 mm to 100 mm. In the SCIG group, headache reached a median peak value of just 1 (range 0 to 13) mm at day six, versus a median peak value of 11 (range 0 to 96) in the IVIG group at day four. Nausea experience in the SCIG group had a stable median value of 0 (range 0 to 21) at all days, compared to a peak value of 3 (range 0 to 90) reached at day four in the IVIG group. For both headache and nausea, this reduced median severity favoring SCIG was highly significant ($p < 0.0001$). Just as important, the peak severity experienced by any patient was also sharply lower in the SCIG group.[11]

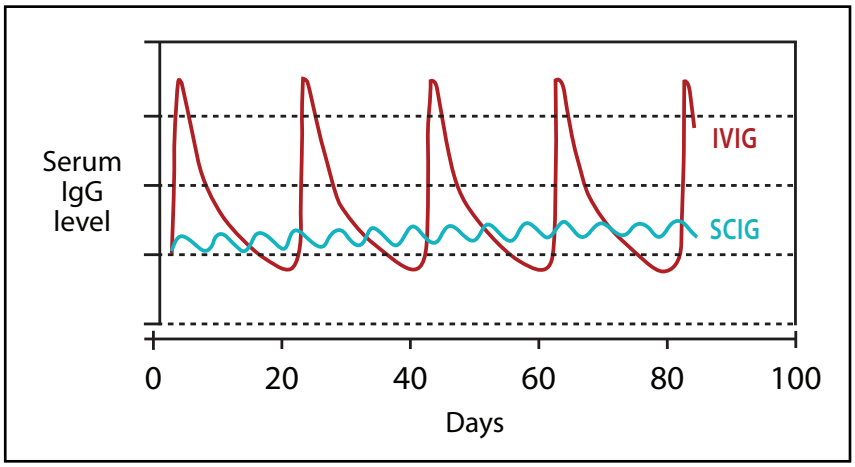
A Better Alternative to Ports or Catheters

A small percentage of CIDP patients prescribed maintenance IVIG therapy either have pre-existing venous access problems or develop them with repeated peripheral intravenous access. Permanent indwelling venous catheters or infusion ports implanted under the skin were once a very popular means to resolve this venous access problem.[12]

Unfortunately, these venous access devices inherently present a significant risk of infection. Localized tissue reaction produced by these devices makes it easier for bacteria and other microorganisms to become established and develop into an active infection. Some types of infections, in particular colonization with Candida albicans, frequently require removal of the port or catheter. Skin bacteria can also gain entry to the port through the needle puncture site, then travel down the catheter lumen to the vein, potentially causing a systemic infection.

A second significant concern is the potential for ports or indwelling catheters to promote thrombus formation, amplifying the risk of a thromboembolic event

Figure. Frequent SCIG self-infusion results in much smaller serum IgG peaks than IVIG infusion of a similar dose every 3 to 4 weeks.



Source: Berman K. Under The Skin Is In. *BioSupply Trends Quarterly*, October 2011, pp 52-54.

rarely associated with administration of IVIG itself.[13]

Citing these known risks of infection and thrombosis, a recently published American Academy of Allergy, Asthma and Immunology practice policy statement recommended that "the placement of permanent central venous access [devices] solely for the purpose of IVIG administration should be discouraged," particularly given the "growing availability of subcutaneous IgG infusion."[14]

Reduced Wearing-Off Effect

Exogenous IG therapy is known to be effective only as long as the supplemental IgG serum level is maintained in the therapeutic range. Some patient responders on maintenance IVIG therapy experience a diminution in muscle strength over the days immediately preceding their upcoming scheduled IVIG infusion. This "wearing off" effect is attributable to a drop-off in serum IgG to below the therapeutic threshold level prior to the next scheduled IVIG infusion — a phenomenon that is averted by frequent IgG dosing used by patients on SCIG therapy.

In a recent crossover study, one-quarter of subjects who reported a preference for SCIG cited the advantage of less fluctuation in muscular strength than they experienced on IVIG therapy. This is unsurprising as small, frequent SCIG doses result in a more consistent serum IgG level, in particular a higher IgG trough level than the trough level shortly prior to the next IVIG infusion (Figure). While the problem of waning muscle strength in the days prior to the next IVIG infusion can also be addressed by increasing the IVIG dose or reducing the interval between IVIG infusions, both of these strategies have downsides that can be averted by switching to SCIG therapy.

Customizing the SCIG Infusion Regimen Is Key

Whether the product is IVIG or SCIG, CIDP patients on maintenance therapy are typically prescribed a total dose of at least 1 g/kg of IgG every three to four weeks. Thus, an 80 kilogram adult prescribed 1 g/kg of 20% SCIG product each four weeks must use an infusion pump to self-administer a total of 400 mL of fluid under the skin over that period. Prescribing instructions for Hizentra specify that, as tolerated, up to a maximum of 50 mL may be infused in each site (abdomen, thigh, upper arm or side of upper leg/hip). In a given session, patients can concurrently infuse their product through up to eight needles placed in different areas of the body. So, in theory, a patient able to tolerate 50 mL in a single infusion site could self-administer 100 mL in just one session each week using just two needles placed in two separate sites on the body. But for most CIDP patients, the maximum tolerated single-site infused volume is much lower than 50 mL.

> "In a recent crossover study, one-quarter of subjects who reported a preference for SCIG cited the advantage of less fluctuation in muscular strength than they experienced on IVIG therapy."

To meet their prescribed weekly SCIG volume, patients face a choice: They can elect either to 1) increase the number of needles and sites they use in each infusion session, or 2) use fewer needles and increase the number of infusion sessions

each week. While most patients settle on two to three infusions per week, "the balance between how many needles to use in a session versus how often to self-infuse is highly individual," said Amy Ehlers, NuFACTOR Specialty Pharmacy's director of pharmacy. "Patients need time to learn and become comfortable with the experience of self-administering SCIG before they decide what works best. If patients are pushed to try a lot of needles or volume in the early stages, some will rebel."

activities, better general health and improved treatment satisfaction; more than 80 percent preferred the subcutaneous route, and 90 percent preferred the home treatment setting. Two-thirds of group B patients treated at home with IVIG followed by SCIG stated their preference for the subcutaneous route.

Results from a more recent IVIG-versus-SCIG preference study in a CIDP patient cohort echo the PI study findings.[3] Twenty of 29 CIDP patients who crossed

> "For many patients, SCIG is also valued for the freedom it offers to self-treat on their own schedule, or for independence from reliance on nurses and other medical professionals."

Independence and Scheduling Flexibility

While relief from systemic side effects is an important reason patients cite for switching from IVIG to SCIG, for many patients, SCIG is also valued for the freedom it offers to self-treat on their own schedule, or for independence from reliance on nurses and other medical professionals. This has been documented in multiple PI patient studies, including a seminal 2006 investigation of the impact of SCIG on health-related quality of life (HRQoL) in 28 PI patients previously treated with IVIG in a clinic setting (group A) and 16 others previously on IVIG therapy at home (group B).[15] After switching to SCIG therapy, group A reported significantly less limitation in their work and daily

over from effective IVIG therapy to SCIG indicated they preferred SCIG therapy. Sixteen of these 20 patients cited increased infusion scheduling flexibility as a reason. More stable strength, milder side effects and time savings were cited as reasons by five, three and two patients, respectively.

It is too early to speculate about what eventual proportion of CIDP patients who require chronic maintenance therapy will elect to switch to SCIG therapy in lieu of remaining on IVIG. Some CIDP patients are needle-phobic or are otherwise uncomfortable with the steps required to self-administer the drug. Others may have residual fine motor control deficits or other issues that preclude this option.

But the experience of the PI population might provide some insight about the prospects for SCIG as maintenance therapy for CIDP: Little more than a decade after the 2006 approval of the first SCIG treatment, SCIG is now the IgG replacement therapy of choice for more than one-half of PI patients in the United States. ❖

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Despite her aversion to using drugs, Angela Matthews says the only reason she survived stage 3 ovarian cancer is because she was prescribed medical marijuana, which enabled her to eat while undergoing chemotherapy treatments.

Medical Marijuana: *A Patient's Perspective*

By Trudie Mitschang

PRIOR TO being diagnosed with ovarian cancer, Angela Matthews says she was about as straitlaced as they came. For her, the very idea of using marijuana for any reason was simply out of the question, until a recommendation from her chemotherapy nurse opened her eyes to its lifesaving potential.

BSTQ: Tell us about the events leading up to your experience with medical marijuana.

Angela: I have never had the desire to use drugs, and I have avoided them my whole life. I am 46 years old and still have never smoked a cigarette. So, when I was told about medicinal marijuana after being diagnosed with stage 3 ovarian cancer, I thought: Not now, not ever. I had seven different prescriptions to help me with the chronic pain and nausea that hit me after my nine-hour surgery and first round of chemo. The problem was none of them worked. After a month of this ordeal, I was down to 100 pounds and was told if I lost any more weight, they were going to have to stop treatment. I still had five more rounds of chemo to go, and it was way too early for this wife and mother of four to give up the fight.

BSTQ: How did your doctor decide medical marijuana might be the right treatment?

Angela: My chemo nurse knew I was dealing with the combination of severe abdominal pain and nausea, which made it impossible for me to eat. She told me her mom battled leukemia and had the same issues with eating. Medical marijuana is what enabled her to eat again. I spoke with my oncologist, and she suggested we give it a try.

BSTQ: What was your prescription?

Angela: The prescription was for medical cannabis, which is very general. The doctor who prescribed it left it up to me to choose which kind. In California, you can't get medical marijuana from the place that prescribes it; you have to take your prescription to a dispensary. I called and explained my symptoms and told them I was a mother of four young kids and I didn't want to feel "loopy." I wanted something that I didn't have to smoke to help with pain management, appetite and nausea. The dispensary employee suggested I go with drops that I could put in my protein shakes and an edible product in the form of a dark chocolate almond candy bar. They contained equal ratios of CBD (cannabidiol) and TCH (tetrahydrocannabinol) strains to give me the appetite and pain relief I needed without feeling "euphoric," as the dispensary employee put it.

BSTQ: How did you react to the treatment?

Angela: I had not eaten much for so long that I had to set a timer to remind myself. The first time the alarm went off for my snack time, I opened a bag of almonds and not only did I eat them all, there was no stomach pain! The same thing happened for lunch and all the other times my alarm went off. I was eating again, and my stomach didn't hurt. All this within hours of drinking my shake with the special ingredient.

BSTQ: What other changes did you notice?

Angela: I still did not have a big appetite, but the marijuana gave me enough relief from my nausea and stomach pain to eat every meal and every snack. I felt the strength coming back into my body almost instantly. I also ate half a square of my candy bar before bed to help with sleep and pain at night.

BSTQ: How long were you on the treatment?

Angela: I kept up this pattern for each round of treatment. During the weeks I received chemo, I took the drops in the morning and ate half a square of chocolate at night. Some days, I needed a little more, but this seemed to be the right formula. I used the medical marijuana for five rounds of chemo for roughly three months.

BSTQ: Did your personal experience with medical marijuana change your view of how it is used?

Angela: I don't know what would have happened if medical marijuana was not available to me. I could have found other options, but who knows how long that would have taken or how much pain or weight loss I would have endured. I am so grateful for this quick and easy solution. Had it not been for marijuana, I don't know if I would have survived. Medical marijuana is not legal in every state. It's sad to think I may not have beat cancer if I lived in a state where medical marijuana was not an option. I think the biggest lesson learned was letting go of the stigma. If a drug is legal and available, there should be no shame in taking it to survive sickness or cope with pain. ❖

Dr. David Casarett changed his position on the use of medical marijuana after conducting extensive research and authoring the book Stoned: A Doctor's Case for Medical Marijuana. *Today, he continues to research when and how to use medical marijuana safely.*

Medical Marijuana:
A Physician's Perspective

FEW SUBSTANCES have been as hotly debated as medical marijuana. Opponents claim it's addictive, carcinogenic and a gateway to more serious drug use. Proponents, on the other hand, say its benefits outweigh the risks, citing it as an effective treatment for everything from cancer, anorexia, AIDS and chronic pain to migraines, arthritis and insomnia. Enter David Casarett, MD, MA, a palliative care physician and researcher who has found himself on both sides of the debate. The author of *Stoned: A Doctor's Case for Medical Marijuana*, Dr. Casarett is a professor of medicine at Duke University and the chief of palliative care at Duke Health.

BSTQ: Where did the idea for your book originate?

Dr. Casarett: The idea came from a patient — a retired English professor — who came to me for help with managing symptoms of advanced cancer. She asked me whether medical marijuana might help her. I started to give her my stock answer: Marijuana is an illegal drug that doesn't have any proven medical benefits, etc. But she pushed me to be specific, in much the same way she probably used to push her students. Eventually, I admitted I didn't know, but I'd find out. My book is the result of that research.

BSTQ: What is the biggest misconception about marijuana in the medical community?

Dr. Casarett: Probably that it offers no medical benefits. Actually, there have been some good studies that have shown very real benefits for some symptoms. True, there isn't as much evidence as I'd like. But, there will be more. New research is coming online every year, and we're gradually figuring out whether and how marijuana works.

BSTQ: What changed your personal perspective on marijuana?

Dr. Casarett: The moment came when I realized there were medical benefits. For me, that flipped the debate. Now we were talking about a substance that has benefits and risks, not just risks. And, in my mind, that put cannabis in the same box as many other legal drugs I prescribe. Once I realized medical cannabis offers benefits, the question became whether, when and how to use it safely, rather than how to ban it.

BSTQ: What is the most prevalent misinformation on both sides of the debate?

Dr. Casarett: From pro-cannabis groups, there are two. One is, because cannabis is a flower, it's perfectly safe. Heroin is derived from poppies, which are also flowers. Heroin isn't safe. Also, pro-cannabis groups advise using cannabis to cure cancer. I met a woman in Denver who put all of her hope in cannabis oil to treat her curable lymphoma; she died six months later. From the anti-cannabis groups, I worry about case reports of risks. For instance, there are reports of people who used cannabis right before they had a stroke. That's a correlation, but it doesn't mean cannabis caused the stroke. It's easy to get those sorts of case reports published.

BSTQ: What's your opinion on theories that cannabis can be used to cure opioid addiction?

Dr. Casarett: There are some theoretical advantages of replacing opioid addiction with cannabis. Cannabis is also addictive, but without the risk of fatal overdose. Still, you have to be careful when talking about replacing one drug with another. The opioid epidemic is one example. Many physicians argued 15 years ago that we needed to do a better job of treating pain and shouldn't be concerned about addiction. We know how that turned out: more opioid prescribing, more availability and, when we tightened the reins, patients went from legal Oxycontin to illegal Oxycontin to heroin. If we get a lot of people to switch from opioids to cannabis, maybe there will be other problems down the road.

BSTQ: What do you think the future holds for medical marijuana?

Dr. Casarett: For me, some of the most exciting advances in the science of medical marijuana are related to what marijuana tells us about the endocannabinoid system, which is the system of hormones, neurotransmitters and receptors in all people. We don't know a lot about what that system does, but we do know marijuana works by tapping into that system. The cannabinoids in marijuana trick the body by mimicking naturally occurring endocannabinoids like anandamide. While it's fascinating to think about what marijuana could do, and although clinical trials of marijuana are essential, the really neat science of the future may focus on that endocannabinoid system: what it does, how it works and how we can use it to promote health. ❖

TRUDIE MITSCHANG is a contributing writer for *BioSupply Trends Quarterly* magazine.

Ten Great Online Resources for Physicians

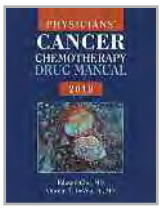
Author: AMA Insurance Agency

This online site provides descriptions and links to the top-10 resources for physicians, including KevinMD Medical blog, Paging Dr. Gupta, Doctors Without Borders YouTube Channel, The Disease Management Care blog, Epocrates smartphone app, top health-related blogs on Technorati, 33 Charts, most Dugg articles with the keyword "medicine" on Digg, Mayo Clinic Center for Social Media and the American Medical Association's Insurance Agency's Post Scripts blog.

www.amainsure.com/physicians-in-focus/ten-great-online-resources-for-physicians.html

Physicians' Cancer Chemotherapy Drug Manual 2019, 19th Edition

Authors: Edward Chu, MD, and Vincent T. DeVita Jr., MD



Completely revised and updated for 2019, the *Physicians' Cancer Chemotherapy Drug Manual* is an up-to-date guide to the latest information on standard therapy and recent advances in the field. Written by world-class experts in clinical cancer therapeutics, this reference provides a complete, easy-to-use catalog of more than 100 drugs and commonly used drug regimens — both on- and off-label — for treatment of all major cancers. The release date for this book is Dec. 17, but it can be preordered.

www.amazon.com/Physicians-Cancer-Chemotherapy-Drug-Manual/dp/1284168476/ref=sr_1_sc_3?s=books&ie=UTF8&qid=1532621342&sr=1-3-spell&keywords=physician+manua

Chronic Care Management Toolkit

Author: American College of Physicians

This downloadable resource describes what practices need to implement and bill chronic care management (CCM) codes. Sections include understanding CCM, CCM definitions, CCM codes, guidelines for billing and documentation, eight steps to implement CCM codes, a sample log of CCM patients, a sample letter to patients with two or more chronic care conditions, a sample welcome letter to patients and visit checklist, and a sample CCM stop form.

www.acponline.org/system/files/documents/running_practice/payment_coding/medicare/chronic_care_management_toolkit.pdf

Top Trends in Drug and Device Advertising and Promotion

Author: U.S. Food and Drug Administration

This book explores the six areas regulators give the most attention to drug and device advertising and promotion: 1) consistent communication: three factors that ensure communications are consistent with a product's approved labeling; 2) direct-to-consumer advertising: use of distracting visuals, competing superimposed images and lively music that can minimize the required presentation of risk information; 3) risk disclosure: how much information needs to be presented and how; 4) payer communications: disseminating healthcare economic information to payers postapproval; 5) preapproval promotion: a new safe harbor for communicating information about investigational products to payers; and 6) transparency: making it clear that a communication is sponsored advertising.

www.fdanews.com/products/56085-top-trends-in-drug-and-device-advertising-and-promotion-enforcement-priorities-for-the-fda-and-ftc

A Guide to Telemedicine for the Physician Practice

Authors: Kerry Ann Hayon, MHA, and Jillian Pedrotty, MHA

As telemedicine continues to surge in popularity and more organizations decide to engage in different technologies, a number of practice management strategies should be considered prior to implementation. This guide explores the challenges and benefits, while providing practical considerations for physicians and physician practices that may be interested in engaging in telemedicine.

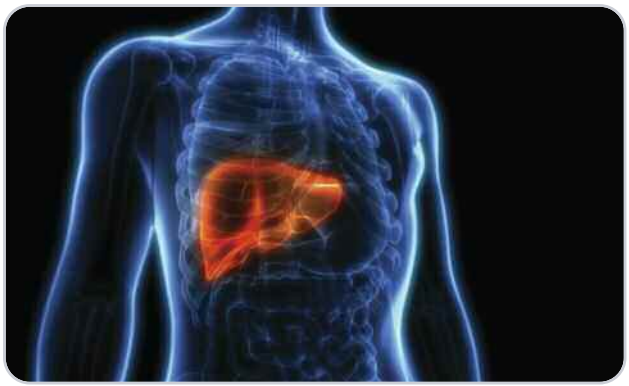
www.massmed.org/Physicians/Practice-Management/Practice-Ownership-and-Operations/Guide-to-Telemedicine-for-Physician-Practice-(pdf)

Chronic Human Albumin Therapy Prolongs Survival in Patients with Decompensated Cirrhosis

Results from a large multicenter, randomized, parallel, open-label clinical trial conducted in 33 academic and nonacademic Italian hospitals have led a team of Italian investigators to conclude adding long-term administration of human albumin to conventional treatment in patients with decompensated cirrhosis appears to prolong survival.

From April 2011 to May 2015, 440 patients with cirrhosis and uncomplicated ascites who were treated with anti-aldosteronic drugs and furosemide were enrolled and randomly assigned to receive either standard medical treatment (SMT) or SMT plus 40 grams of human albumin twice weekly for two weeks, followed by 40 grams weekly for up to 18 months.

Thirty-eight of 218 patients died in the SMT plus human albumin group (17.4%), compared to 46 of 213 patients in the SMT group (21.6%). Overall 18-month survival was significantly higher in the SMT plus human albumin group than in the SMT-only group (Kaplan-Meier estimates 77% vs. 66%; p=0.028), as reflected in a 38 percent reduction in the mortality hazard ratio (0.62, 95 confidence interval, 0.40–0.95). The rate of grade three to four non-liver-related adverse events was identical (22%) in both treatment groups.



The investigators proposed that chronic administration of human albumin might prolong survival in decompensated cirrhosis patients by acting as a disease-modifying treatment.

Caraceni P, Riggio O, Angeli P, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet *2018 Jun 16;391(10138):2417-29.*

Frequency-Escalated Prophylaxis for Severe Hemophilia A Reduces Clotting Factor Usage with Minimal Long-Term Arthropathy

Tailored frequency-escalated prophylaxis results in minimal long-term arthropathy and very good health outcomes, while reducing the quantity of costly clotting factor as compared with standard prophylaxis protocols, according to a 16-year longitudinal study of Canadian boys with severe hemophilia A.

Between June 1997 and January 2007, 12 centers participating in the Canadian Hemophilia Prophylaxis Study enrolled 56 boys ages 1.0 years to 2.5 years, and followed them for a median of 10.2 years. Study participants were treated with standard half-life recombinant factor VIII, beginning as once-weekly prophylaxis at 50 IU/kg and escalating in frequency (with accompanying dose adjustments) in response to breakthrough bleeding as determined by the protocol. The primary endpoint was joint health, as measured at study end by the modified Colorado Child Physical Examination Scores (CCPES).

The median end-of-study CCPES physical examination score was 1 (IQR 1-3; range 0-12) for the left ankle and 1 (IQR 1-2; 0-12) for the right ankle, with all other joints having a median score of 0. No treatment-related safety events occurred over the course of the study. The median annualized index joint bleeding rate was 0.95 per year (IQR 0.44-1.35; range 0.00-13.43), but 17 (30%) patients had protocol-defined unacceptable breakthrough bleeding at some point during the study.

While concluding that tailored frequency-escalated prophylaxis leads to very little arthropathy and a reduced quantity of clotting factor as compared to standard prophylaxis, the investigators called for future studies employing a more stringent protocol to address some bleeding sequelae still observed in this study.

Feldman BM, Rivard GE, Babyn P, et al. Tailored frequency-escalated primary prophylaxis for severe haemophilia A: results of the 16-year Canadian Hemophilia Prophylaxis Study longitudinal cohort. Lancet Haematol *2018 Jun;5(6):e252-260.*

Medicare Immune Globulin Reimbursement Rates

Rates are effective October 1, 2018, through December 31, 2018

	Product	Manufacturer	HCPCS	ASP + 6% (before sequestration)	ASP + 4.3%* (after sequestration)
IVIG	FLEBOGAMMA	Grifols	J1572	$70.13	$69.01
	GAMMAGARD SD	Shire	J1566	$75.89	$74.67
	GAMMAPLEX	BPL	J1557	$104.13	$102.46
	OCTAGAM	Octapharma	J1568	$73.44	$72.27
	PRIVIGEN	CSL Behring	J1459	$79.27	$77.99
IVIG/SCIG	GAMMAGARD LIQUID	Shire	J1569	$86.28	$84.90
	GAMMAKED	Kedrion	J1561	$78.98	$77.72
	GAMUNEX-C	Grifols	J1561	$78.98	$77.72
SCIG	CUVITRU	Shire	J1555	$133.97	$131.82
	HIZENTRA	CSL Behring	J1559	$98.60	$97.02
	HYQVIA	Shire	J1575	$141.25	$138.98

* Reflects 2% sequestration reduction applied to 80% Medicare payment portion as required under the Budget Control Act of 2011.

Calculate your reimbursement online at www.FFEnterprises.com.

Immune Globulin Reference Table

	Product	Manufacturer	Indication	Size
IVIG	FLEBOGAMMA 5% DIF Liquid	Grifols	PI	2.5 g, 5 g, 10 g, 20 g
	FLEBOGAMMA 10% DIF Liquid	Grifols	PI, ITP	5 g, 10 g, 20 g
	GAMMAGARD S/D Lyophilized, 5% (Low IgA)	Shire	PI, ITP, B-cell CLL, KD	5 g, 10 g
	GAMMAPLEX Liquid, 5%	BPL	PI, ITP	5 g, 10 g, 20 g
	GAMMAPLEX Liquid, 10%	BPL	PI, ITP	5 g, 10 g, 20 g
	OCTAGAM Liquid, 5%	Octapharma	PI	1 g, 2.5 g, 5 g, 10 g
	OCTAGAM Liquid, 10%	Octapharma	ITP	2 g, 5 g, 10 g, 20 g
	PRIVIGEN Liquid, 10%	CSL Behring	PI, ITP, CIDP	5 g, 10 g, 20 g, 40 g
IVIG/SCIG	GAMMAGARD Liquid, 10%	Shire	IVIG: PI, MMN	1 g, 2.5 g, 5 g, 10 g, 20 g, 30 g
			SCIG: PI	
	GAMMAKED Liquid, 10%	Kedrion	IVIG: PI, ITP, CIDP	1 g, 5 g, 10 g, 20 g
			SCIG: PI	
	GAMUNEX-C Liquid, 10%	Grifols	IVIG: PI, ITP, CIDP	1 g, 2.5 g, 5 g, 10 g, 20 g, 40 g
			SCIG: PI	
SCIG	CUVITRU Liquid, 20%	Shire	PI	1 g, 2 g, 4 g, 8 g
	HIZENTRA Liquid, 20%	CSL Behring	PI, CIDP	1 g, 2 g, 4 g, 10 g
	HYQVIA Liquid, 10%	Shire	PI	2.5 g, 5 g, 10 g, 20 g, 30 g

CIDP Chronic inflammatory demyelinating polyneuropathy
CLL Chronic lymphocytic leukemia
ITP Immune thrombocytopenic purpura
KD Kawasaki disease
MMN Multifocal motor neuropathy
PI Primary immune deficiency disease

2018–2019 Influenza Vaccine

Administration Codes: G0008 (Medicare plans)
Diagnosis Code: V04.81

Product	Manufacturer	Presentation	Age Group	Code
Trivalent				
FLUAD (aIIV3)	SEQIRUS	0.5 mL PFS 10-BX	65 years and older	90653
FLUZONE HIGH-DOSE (IIV3)	SANOFI PASTEUR	0.5 mL PFS 10-BX	65 years and older	90662
Quadrivalent				
AFLURIA (IIV4)	SEQIRUS	0.5 mL PFS 10-BX	5 years and older	90686
AFLURIA (IIV4)	SEQIRUS	5 mL MDV	5 years and older	90688
FLUARIX (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLUBLOK (ccIIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	18 years and older	90682
FLUCELVAX (ccIIV4)	SEQIRUS	0.5 mL PFS 10-BX	4 years and older	90674
FLUCELVAX (ccIIV4)	SEQIRUS	5 mL MDV	4 years and older	90756*
FLULAVAL (IIV4)	GSK	0.5 mL PFS 10-BX	6 months and older	90686
FLULAVAL (IIV4)	GSK	5 mL MDV	6 months and older	90688
FLUMIST (LAIV4)	MEDIMMUNE	0.2 mL nasal spray 10-BX	2-49 years	90672
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL PFS 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	0.5 mL SDV 10-BX	3 years and older	90686
FLUZONE (IIV4)	SANOFI PASTEUR	5 mL MDV	6 months and older	90688
FLUZONE PEDIATRIC (IIV4)	SANOFI PASTEUR	0.25 mL PFS 10-BX	6-35 months	90685/90687

aIIV3 MF59-adjuvanted trivalent inactivated injectable
IIV3 Egg-based trivalent inactivated injectable
ccIIV4 Cell culture-based quadrivalent inactivated injectable
IIV4 Egg-based quadrivalent inactivated injectable
LAIV4 Egg-based live attenuated quadrivalent nasal spray
RIV3 Recombinant hemagglutinin trivalent injectable

* Providers should check with their respective payers to verify which code they are recognizing for Flucelvax Quadrivalent 5 mL MDV product reimbursement for this season.

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